

L11 ANSWER 1 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2007:409726 CAPLUS Full-text

DN 146:422017

TI Alkyl 4-[4-(5-oxo-2,3,5,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-8-yloxy)-butyrylamino]-1H-pyrrole-2-carboxylate derivatives and related compounds for the treatment of a proliferative disease and their preparation

IN Howard, Philip Wilson; Thurston, David Edwin; Wells, Geoffrey

PA Spirogen Limited, UK

SO PCT Int. Appl., 119pp.

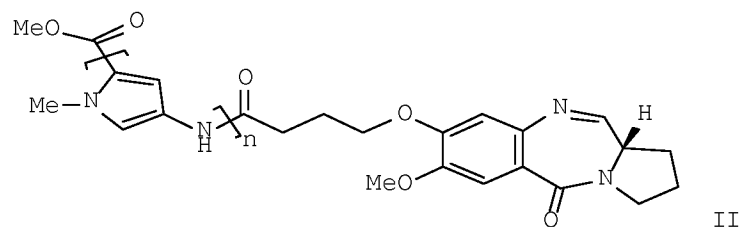
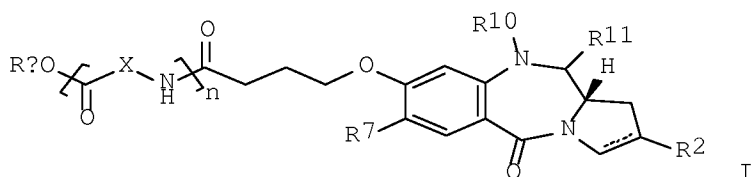
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2007039752	A1	20070412	WO 2006-GB3718	20061005
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
	RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	US 20070154906	A1	20070705	US 2006-544191	20061005
PRAI	US 2005-723681P	P	20051005		
	US 2005-724064P	P	20051006		
OS	MARPAT 146:422017				
GI					



AB The invention relates to compds. of formula I; or a salt or solvate thereof, and their use in the treatment of proliferative diseases. Compds. of formula I wherein the dotted line is an optional double bond; R2 is selected from H, OH, =O, =CH2, CN, R, OR, halo, =CH-R, O-SO2-R, CO2R and COR; R7 is H, R, OH, OR, SH, SR, NH2, NHR, NRR', nitro, Me3Sn and halo; R and R' are independently (un)substituted C1-7 alkyl, C3-20 heterocyclyl and C5-20 aryl groups; R10 and

R11 either together form a double bond, or are selected from H, OH and derivs., SH and derivs. and NH2 and derivs.; X is heteroarylene; and their pharmaceutically acceptable salts and solvates thereof are claimed. The compound is useful for the treatment of proliferative diseases. Example compound II (n = 2) was prepared by deprotection of a Boc-pyrrole dimer followed by amidation with (11aS)-7-methoxy-8-(3-methoxycarbonylpropoxy)-5-oxo-11-(tetrahydropyran-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-pyrrole[2,1-c][1,4]benzodiazepine-10-carboxylic acid allyl ester; the resulting amide underwent decarboxylation and elimination to give compound II. All the invention compds. were evaluated for their antiproliferative activity (data given).

IT 679005-40-4P 679005-41-5P 864672-71-9P  
 864672-72-0P 864672-97-9P 909415-12-9P  
 909415-20-9P 909415-21-0P 909415-22-1P  
 909415-23-2P 909415-24-3P 909415-25-4P  
 934235-10-6P 934235-11-7P 934235-12-8P  
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 934235-25-3P 934235-26-4P 934235-27-5P  
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RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

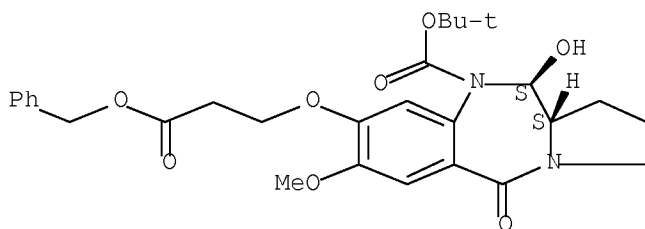
(intermediate; preparation of alkyl

[(oxotetrahydropyrrolobenzodiazepineyl)oxy]butyrylamino]pyrrolecarboxylate derivs. and related compds. for the treatment of a proliferative disease)

RN 679005-40-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(phenylmethoxy)propoxy]-, 1,1-dimethylethyl ester, (11S,11aS)- (CA INDEX NAME)

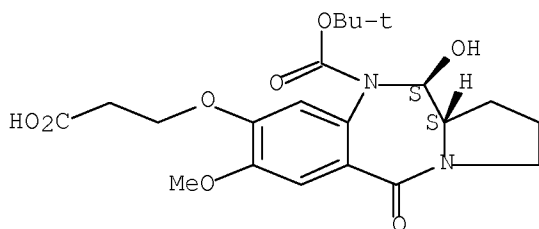
Absolute stereochemistry. Rotation (+).



RN 679005-41-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 10-(1,1-dimethylethyl) ester, (11S,11aS)- (CA INDEX NAME)

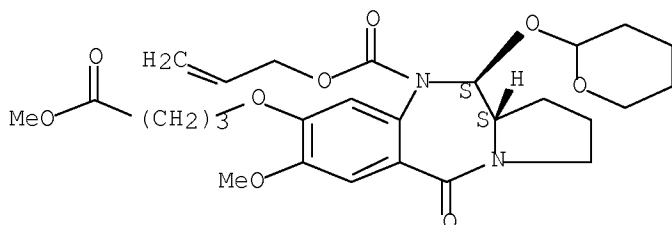
Absolute stereochemistry. Rotation (+).



RN 864672-71-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-8-(4-methoxy-4-oxobutoxy)-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA  
INDEX NAME)

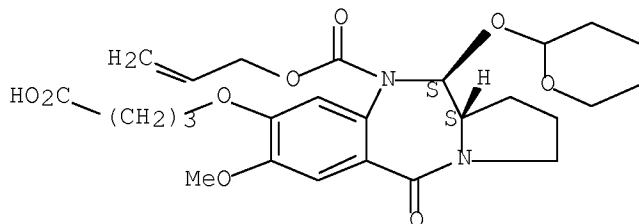
Absolute stereochemistry.



RN 864672-72-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(3-carboxypropoxy)-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-  
2H-pyran-2-yl)oxy]-, 10-(2-propen-1-yl) ester, (11S,11aS)- (CA INDEX  
NAME)

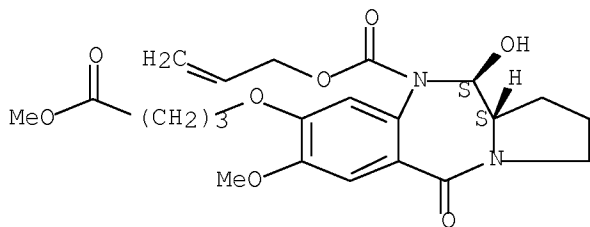
Absolute stereochemistry.



RN 864672-97-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(4-methoxy-4-oxobutoxy)-5-oxo-  
, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

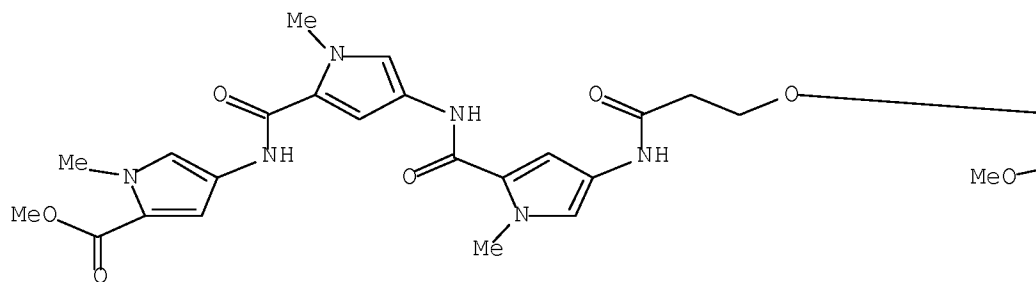


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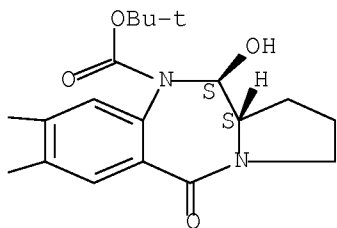
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-[3-[[5-[[[5-[[[5-(methoxycarbonyl)-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-3-oxopropoxy]-5-oxo-, 1,1-dimethylethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

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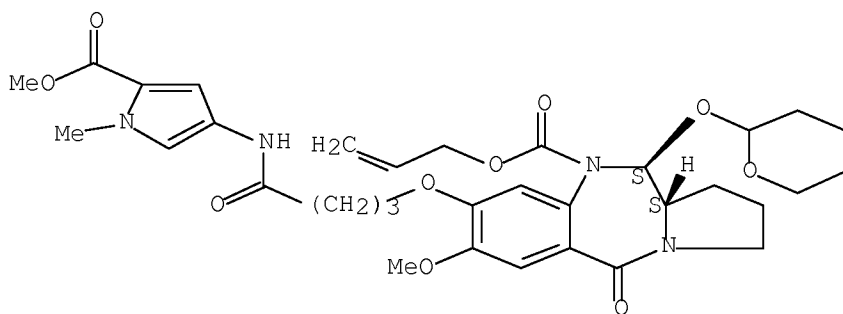


RN 909415-20-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[5-(methoxycarbonyl)-1-methyl-1H-pyrrol-3-yl]amino]-4-oxobutoxy]-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)



Absolute stereochemistry.

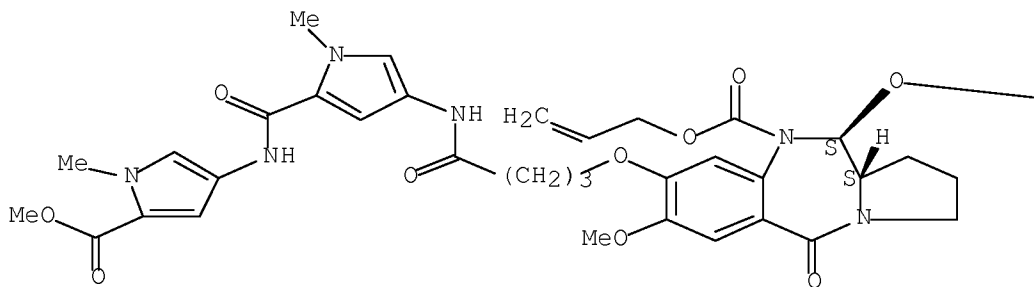


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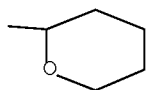
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[5-[[[5-(methoxycarbonyl)-1-methyl-  
1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-4-oxobutoxy]-  
5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester,  
(11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

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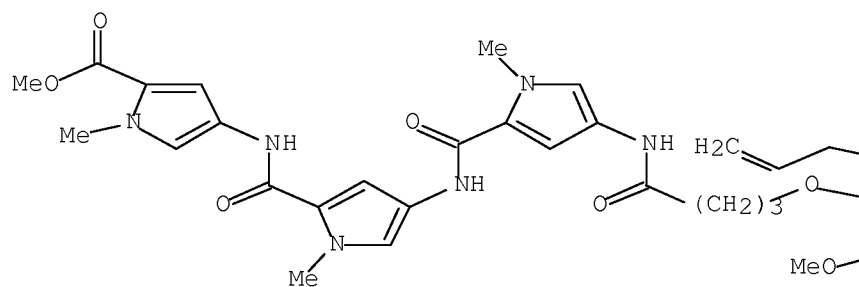


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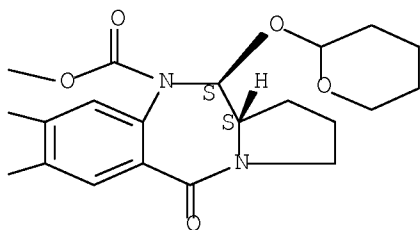
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[5-[[[5-[[[5-(methoxycarbonyl)-1-  
methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-  
yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-4-oxobutoxy]-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA  
INDEX NAME)

Absolute stereochemistry.

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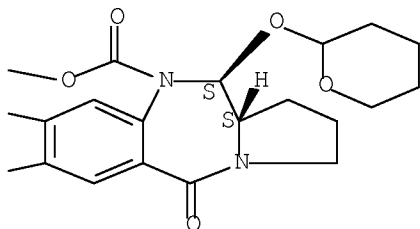
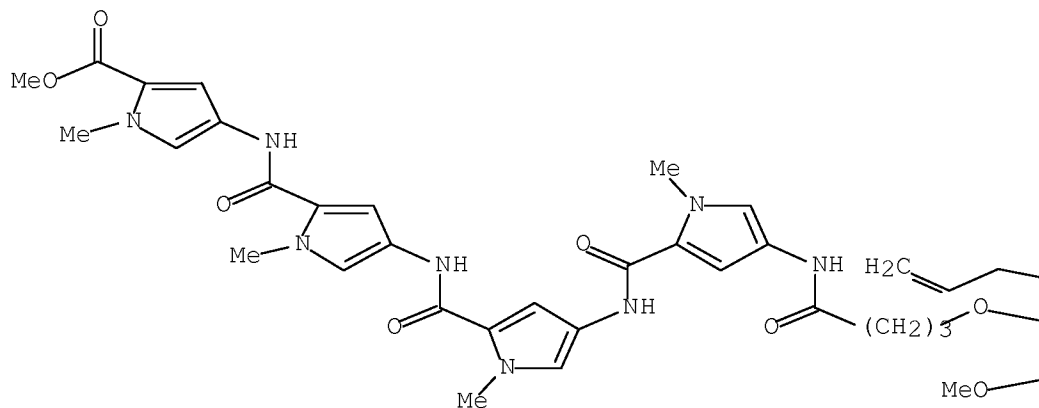


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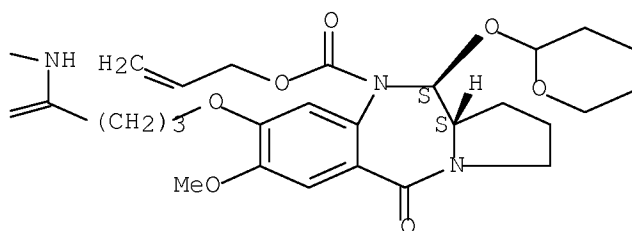
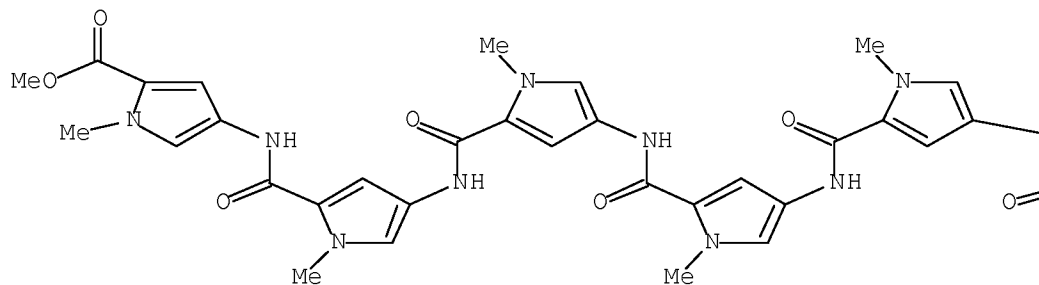
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 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[5-[[[5-[[[5-[[[5-(methoxycarbonyl)-  
 1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-  
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 pyrrol-3-yl]amino]-4-oxobutoxy]-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-,  
 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



RN 909415-24-3 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[[5-[[[5-[[[5-[[[5-[[[5-  
 (methoxycarbonyl)-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-  
 pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-  
 methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-4-  
 oxobutoxy]-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester,  
 (11S,11aS)- (CA INDEX NAME)

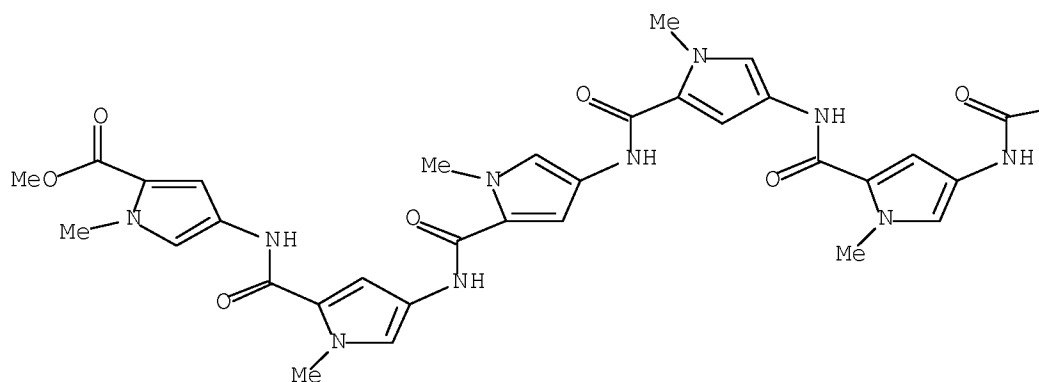
Absolute stereochemistry.

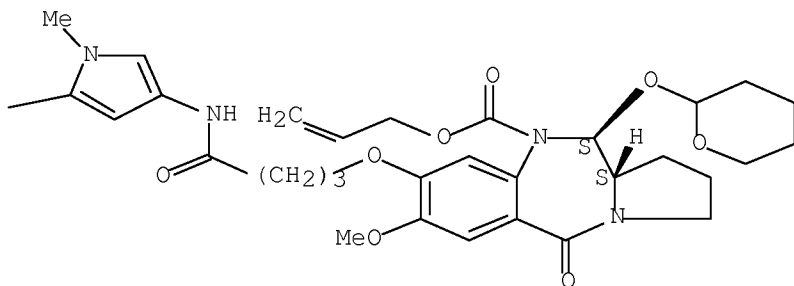


RN 909415-25-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
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(methoxycarbonyl)-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-  
pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-  
methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-  
yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-4-oxobutoxy]-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA  
INDEX NAME)

Absolute stereochemistry.

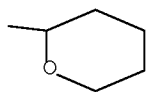
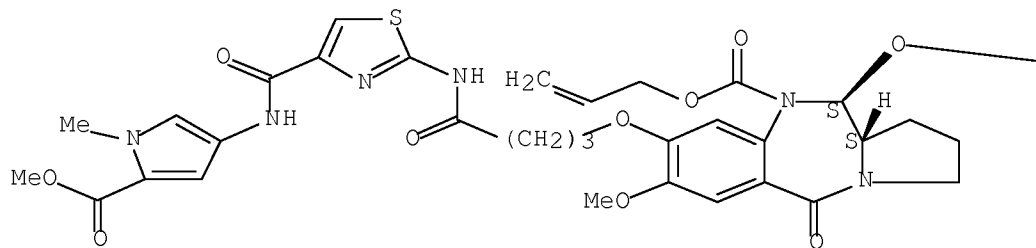




RN 934235-10-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[4-[[[5-(methoxycarbonyl)-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-2-thiazolyl]amino]-4-oxobutoxy]-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

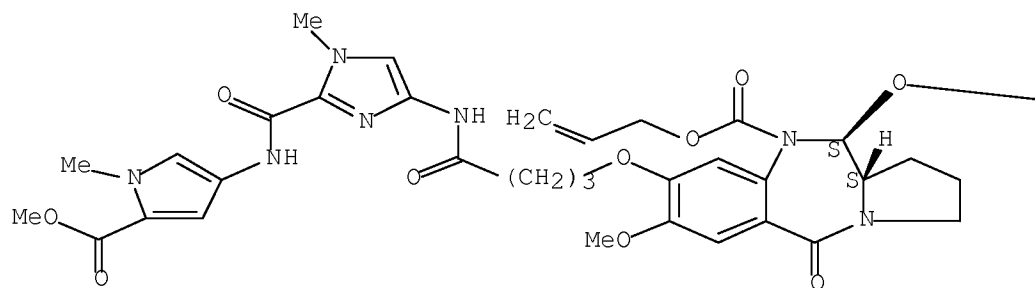


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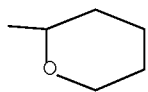
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[2-[[[5-(methoxycarbonyl)-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-imidazol-4-yl]amino]-4-oxobutoxy]-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

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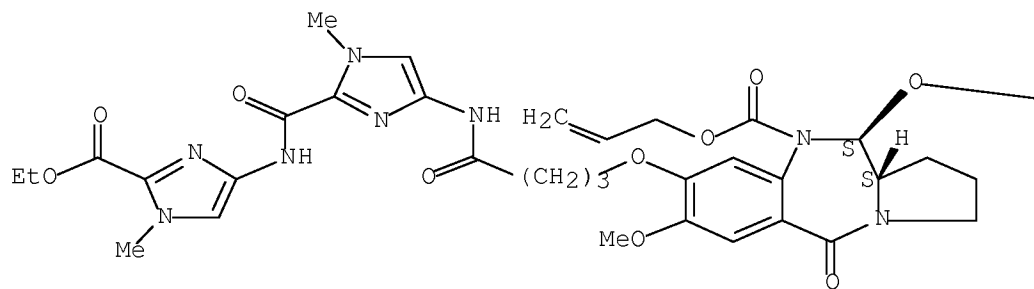
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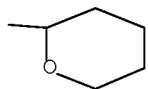


RN 934235-12-8 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[4-[[2-[[[2-(ethoxycarbonyl)-1-methyl-1H-imidazol-4-yl]amino]carbonyl]-1-  
methyl-1H-imidazol-4-yl]amino]-4-oxobutoxy]-2,3,11,11a-tetrahydro-7-  
methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester,  
(11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

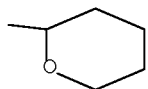
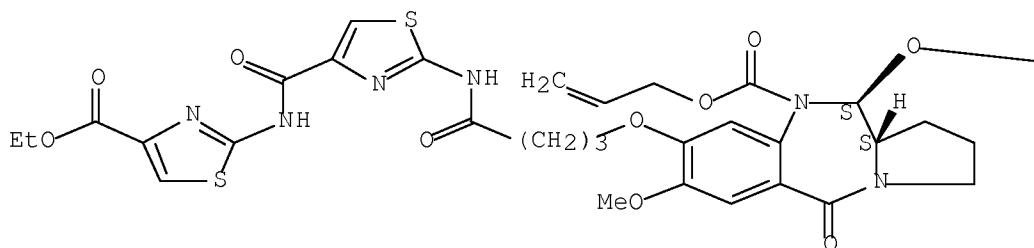
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 8-[4-[[4-[[4-(ethoxycarbonyl)-2-thiazolyl]amino]carbonyl]-2-  
 thiazolyl]amino]-4-oxobutoxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
 [(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA  
 INDEX NAME)

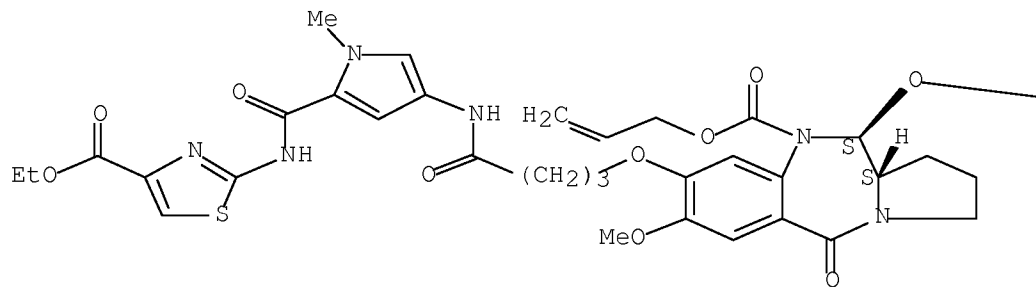
Absolute stereochemistry.



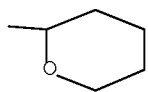
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 pyrrol-3-yl]amino]-4-oxobutoxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
 [(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA  
 INDEX NAME)

Absolute stereochemistry.

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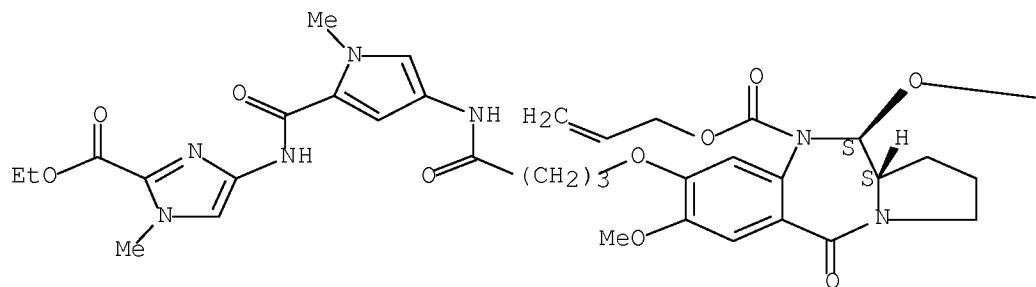
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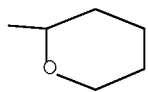
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 methyl-1H-pyrrol-3-yl]amino]-4-oxobutoxy]-2,3,11,11a-tetrahydro-7-methoxy-  
 5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester,  
 (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

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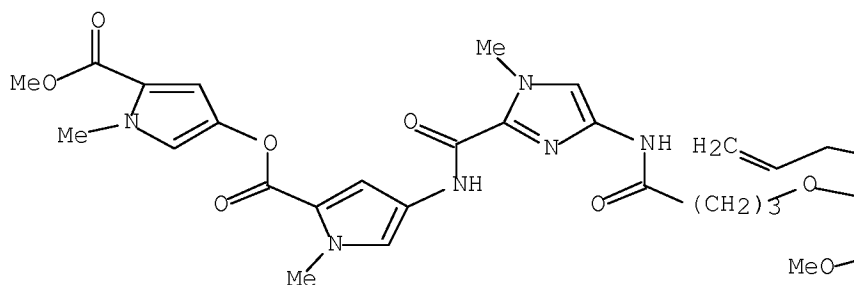


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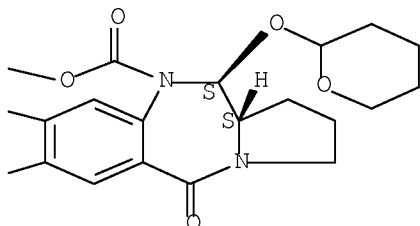
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[2-[[[5-[[[5-(methoxycarbonyl)-1-methyl-1H-pyrrol-3-yl]oxy]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-imidazol-4-yl]amino]-4-oxobutoxy]-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

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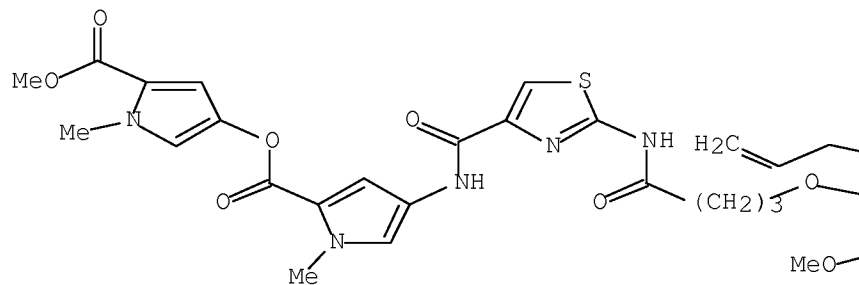


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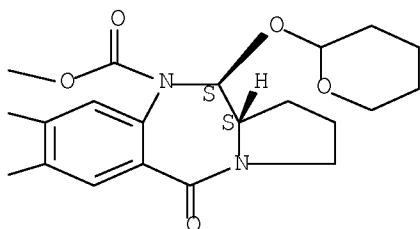
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[4-[[[5-[[[5-(methoxycarbonyl)-1-methyl-1H-pyrrol-3-yl]oxy]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-2-thiazolyl]amino]-4-oxobutoxy]-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

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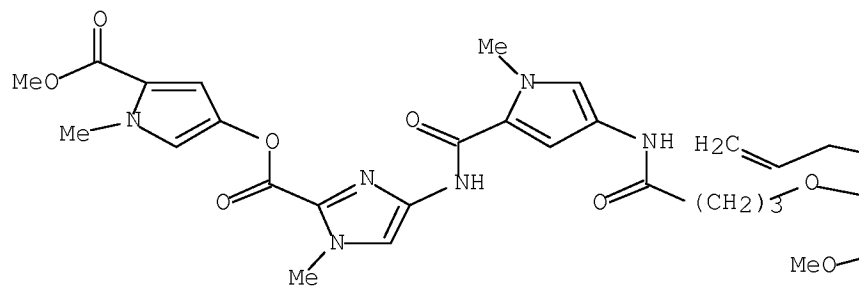
PAGE 1-B

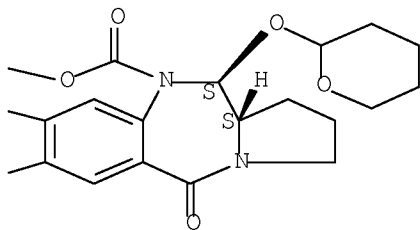


RN 934235-18-4 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[5-[[[2-[[[5-(methoxycarbonyl)-1-  
 methyl-1H-pyrrol-3-yl]oxy]carbonyl]-1-methyl-1H-imidazol-4-  
 yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-4-oxobutoxy]-5-oxo-11-  
 [(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA  
 INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

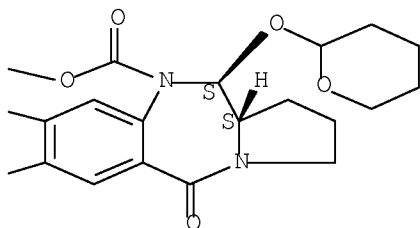
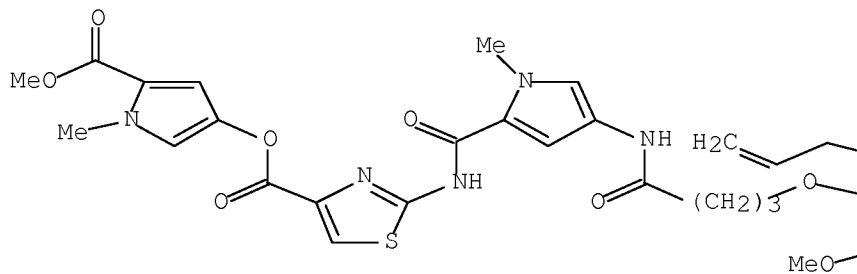




RN 934235-19-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[5-[[[4-[[[5-(methoxycarbonyl)-1-methyl-1H-pyrrol-3-yl]oxy]carbonyl]-2-thiazolyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-4-oxobutoxy]-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

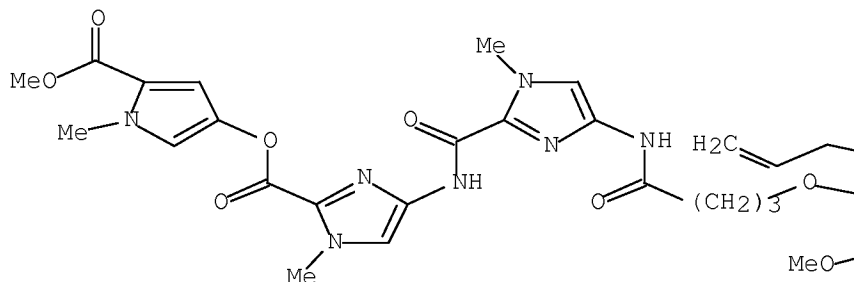


RN 934235-20-8 CAPLUS

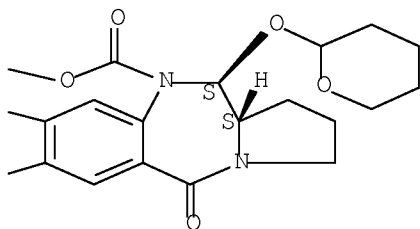
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[2-[[[2-[[[5-(methoxycarbonyl)-1-methyl-1H-pyrrol-3-yl]oxy]carbonyl]-1-methyl-1H-imidazol-4-yl]amino]carbonyl]-1-methyl-1H-imidazol-4-yl]amino]-4-oxobutoxy]-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

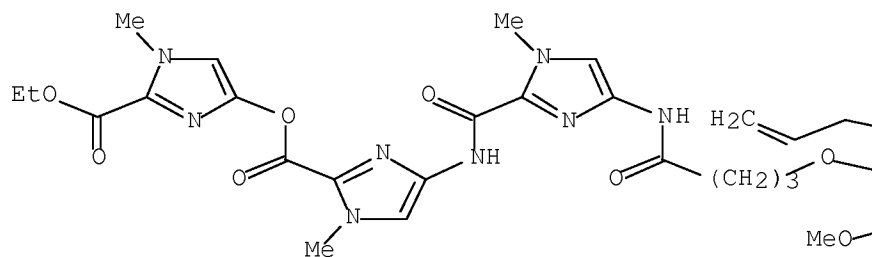


RN 934235-21-9 CAPLUS

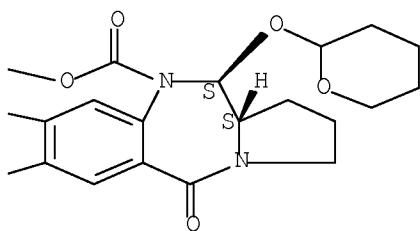
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[4-[[2-[[[2-[[[2-(ethoxycarbonyl)-1-methyl-1H-imidazol-4-yl]oxy]carbonyl]-1-methyl-1H-imidazol-4-yl]amino]carbonyl]-1-methyl-1H-imidazol-4-yl]amino]-4-oxobutoxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



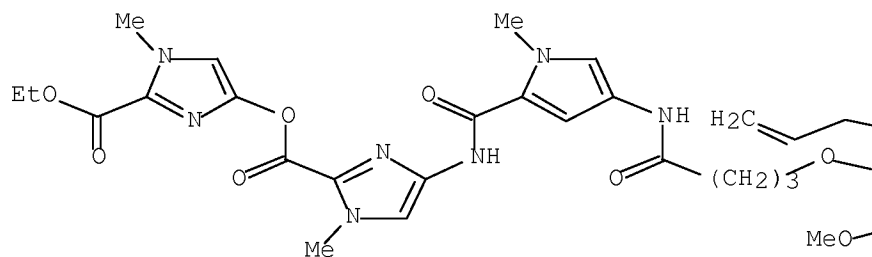
PAGE 1-B

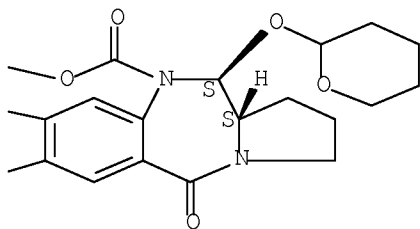


RN 934235-22-0 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
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Absolute stereochemistry.

PAGE 1-A

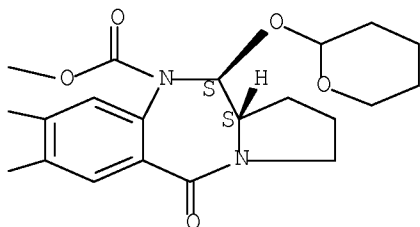
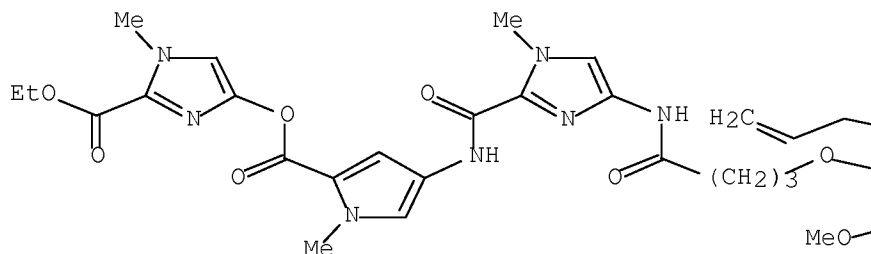




RN 934235-23-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[4-[[2-[[[5-[[2-(ethoxycarbonyl)-1-methyl-1H-imidazol-4-yl]oxy]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-imidazol-4-yl]amino]-4-oxobutoxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



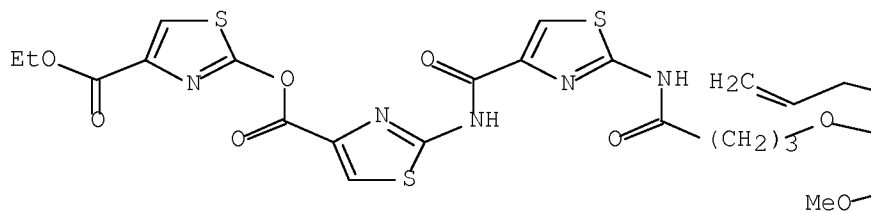
RN 934235-24-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[4-[[4-[[[4-[[[4-(ethoxycarbonyl)-2-thiazolyl]oxy]carbonyl]-2-thiazolyl]amino]carbonyl]-2-thiazolyl]amino]-4-oxobutoxy]-2,3,11,11a-

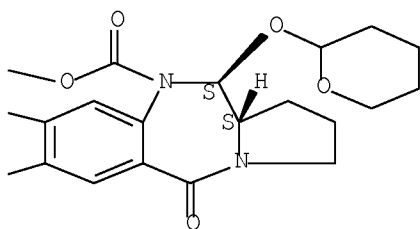
tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-,  
2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

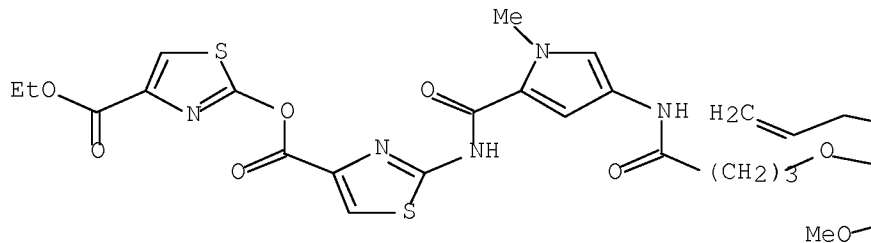


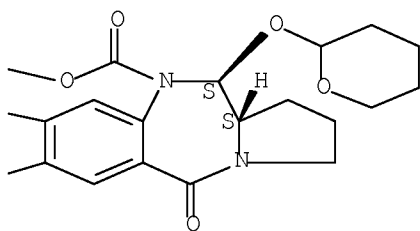
RN 934235-25-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[4-[[5-[[[4-[[[4-(ethoxycarbonyl)-2-thiazolyl]oxy]carbonyl]-2-  
thiazolyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-4-oxobutoxy]-  
2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-,  
2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

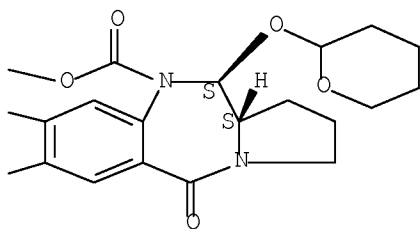
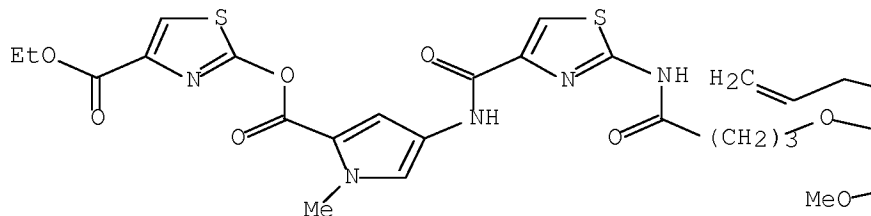




RN 934235-26-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[4-[[[4-[[[5-[[[4-(ethoxycarbonyl)-2-thiazolyl]oxy]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-2-thiazolyl]amino]-4-oxobutoxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



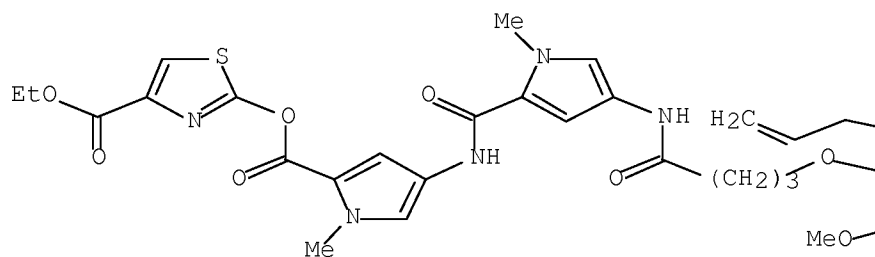
RN 934235-27-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[4-[[[5-[[[5-[[[4-(ethoxycarbonyl)-2-thiazolyl]oxy]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-4-oxobutoxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

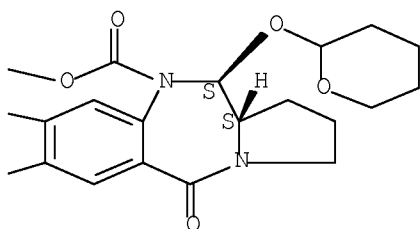
Absolute stereochemistry.



PAGE 1-A



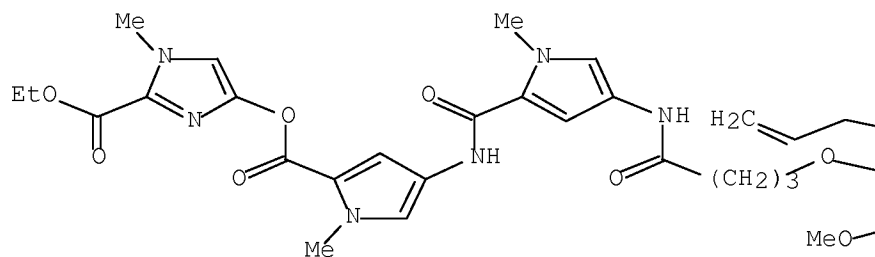
PAGE 1-B

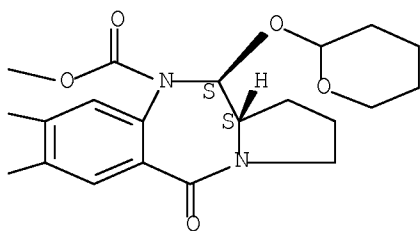


RN 934235-28-6 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-[4-[[5-[[[5-[[[2-(ethoxycarbonyl)-1-methyl-1H-imidazol-4-yl]oxy]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-4-oxobutoxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

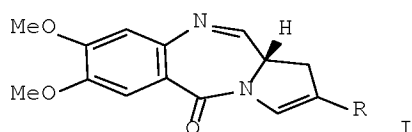
PAGE 1-A





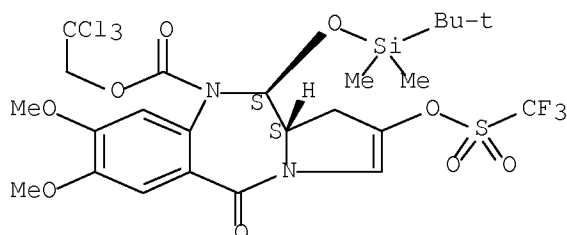
RE.CNT 3      THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2007:360773 CAPLUS Full-text  
 DN 147:9874  
 TI Parallel Synthesis of a Novel C2-Aryl Pyrrolo[2,1-c][1,4]benzodiazepine  
 (PBD) Library  
 AU Antonow, Dyeison; Cooper, Nectaroula; Howard, Philip W.; Thurston, David  
 E.  
 CS Spirogen Limited, London, NW1 0NH, UK  
 SO Journal of Combinatorial Chemistry (2007), 9(3), 437-445  
 CODEN: JCCHFF; ISSN: 1520-4766  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 147:9874  
 GI



AB A 66-membered library of C2-aryl pyrrolo[2,1-c][1,4]benzodiazepines I [R = Ph, 4-MeOC<sub>6</sub>H<sub>4</sub>, 3-H<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 2-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, 4-(4-methyl-1-piperazinyl)phenyl, 2-thienyl, 4-pyridyl, 2-naphthyl, etc.] has been successfully prepared by parallel synthesis via Suzuki coupling using polystyrene-bound Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst and polystyrene-bound diethanolamine as scavenger under microwave irradiation. Library members were obtained in sufficient yields (up to 91%) and purity (85-98% crude) for biol. evaluation.  
 IT 864754-74-5P 864755-16-8P 864755-17-9P  
 864755-18-0P 864755-19-1P 937720-37-1P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (parallel synthesis of aryl-substituted pyrrolo[2,1-c][1,4]benzodiazepine library via Suzuki coupling under microwave irradiation)  
 RN 864754-74-5 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 11-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-11,11a-dihydro-7,8-dimethoxy-5-oxo-2-[[[(trifluoromethyl)sulfonyl]oxy]-, 2,2,2-trichloroethyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

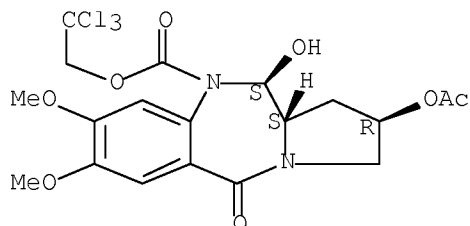
Absolute stereochemistry. Rotation (+).



RN 864755-16-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2-(acetyloxy)-2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-,  
2,2,2-trichloroethyl ester, (2R,11S,11aS)- (9CI) (CA INDEX NAME)

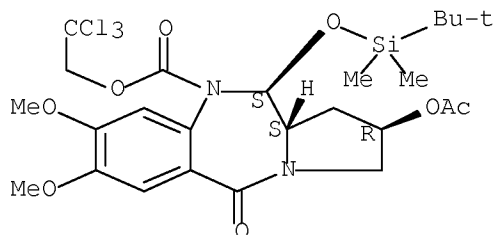
Absolute stereochemistry. Rotation (+).



RN 864755-17-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2-(acetyloxy)-11-[[ (1,1-dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-  
tetrahydro-7,8-dimethoxy-5-oxo-, 2,2,2-trichloroethyl ester,  
(2R,11S,11aS)- (9CI) (CA INDEX NAME)

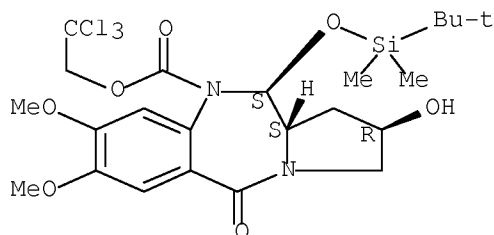
Absolute stereochemistry. Rotation (+).



RN 864755-18-0 CAPLUS

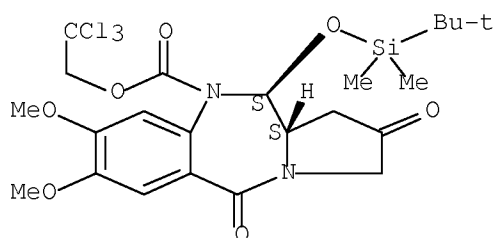
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
11-[[ (1,1-dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-2-hydroxy-  
7,8-dimethoxy-5-oxo-, 2,2,2-trichloroethyl ester, (2R,11S,11aS)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



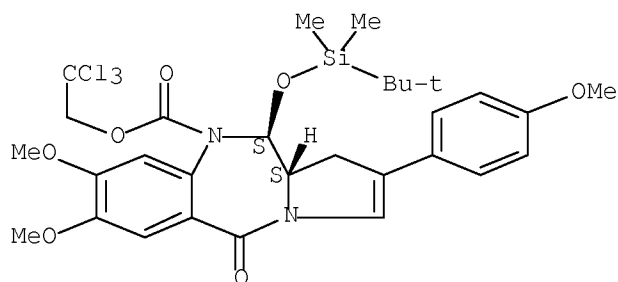
RN 864755-19-1 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 11-[[ (1,1-dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-7,8-  
 dimethoxy-2,5-dioxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (9CI) (CA  
 INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 937720-37-1 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 11-[[ (1,1-dimethylethyl)dimethylsilyl]oxy]-11,11a-dihydro-7,8-dimethoxy-2-  
 (4-methoxyphenyl)-5-oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (CA  
 INDEX NAME)

Absolute stereochemistry.



RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2006:1124678 CAPLUS Full-text  
 DN 145:455035  
 TI Preparation of pyrrolobenzodiazepine derivatives for treatment of  
 proliferative diseases  
 IN Gregson, Stephen John; Howard, Philip Wilson; Chen, Zhizhi  
 PA Spirogen Limited, UK  
 SO PCT Int. Appl., 77pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
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	RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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	CN 101171257	A	20080430	CN 2006-80015716	20071108
	KR 2008004618	A	20080109	KR 2007-727047	20071120
PRAI	GB 2005-8084	A	20050421		
	GB 2005-22746	A	20051107		
	WO 2006-GB1456	W	20060421		
OS	MARPAT 145:455035				
GI					

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The title compds. with general formula I [wherein: R2 = (un)substituted aryl; R6 and R9 = independently H, R, OH, OR, SH, SR, NH2, NHR, NRR', nitro, Me3Sn, or halo, where R and R' = independently (un)substituted alkyl, heterocyclyl, or aryl; R7 = H, R, OH, OR, SH, SR, NH2, NHR, NHRR', nitro, Me3Sn, or halo; Z = alkylene; X = O, S, or NH; n = 2 or 3] or pharmaceutically acceptable salts or solvates thereof are prepared for the treatment of proliferative diseases. For example, compound II•2Na was prepared in a multi-step synthesis. II•2Na showed IC50 of 1.5 nM in the In Vitro cytotoxicity test with K562 human chronic myeloid leukemia cells.

IT 864754-61-0P 864754-66-5P 864755-08-8P  
 864755-09-9P 864755-10-2P 864755-11-3P  
 913262-19-8P 913262-21-2P 913262-23-4P  
 913262-24-5P 913262-26-7P 913262-28-9P

913262-34-7P 913262-35-8P 913262-36-9P

913262-37-0P 913262-38-1P 913262-39-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

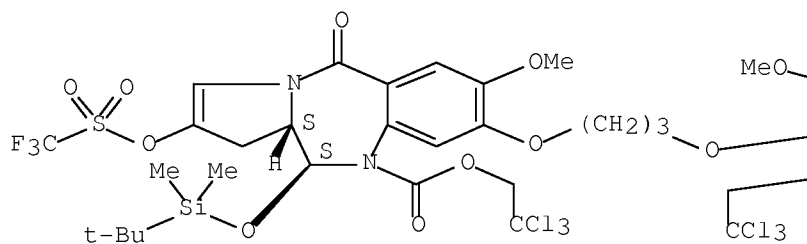
(preparation of pyrrolobenzodiazepine derivs. for treatment of proliferative diseases)

RN 864754-61-0 CAPLUS

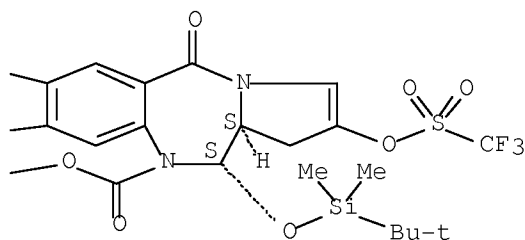
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-11,11a-dihydro-7-methoxy-5-oxo-2-[[[(trifluoromethyl)sulfonyl]oxy]-, bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



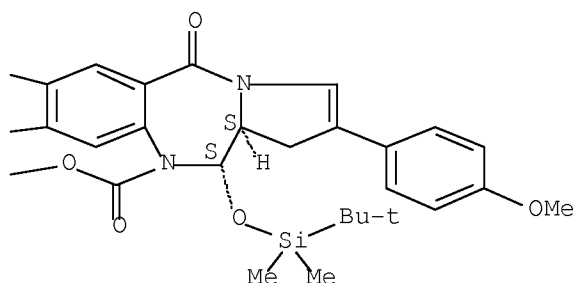
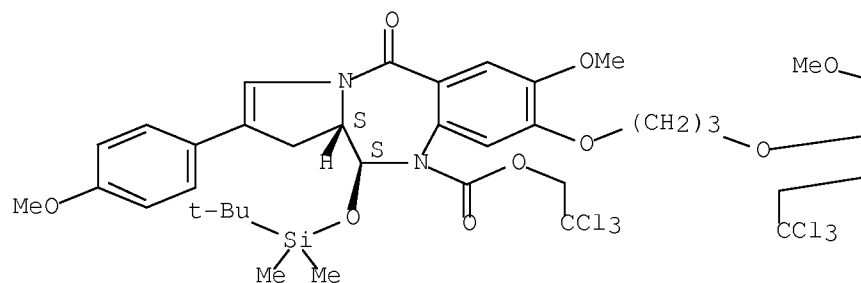
PAGE 1-B



RN 864754-66-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-11,11a-dihydro-7-methoxy-2-(4-methoxyphenyl)-5-oxo-, bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

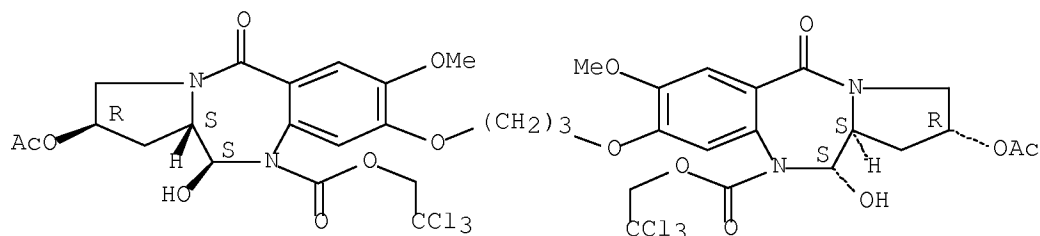
Absolute stereochemistry.



RN 864755-08-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2-(acetyloxy)-2,3,11,11a-tetrahydro-11-  
hydroxy-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester,  
(2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



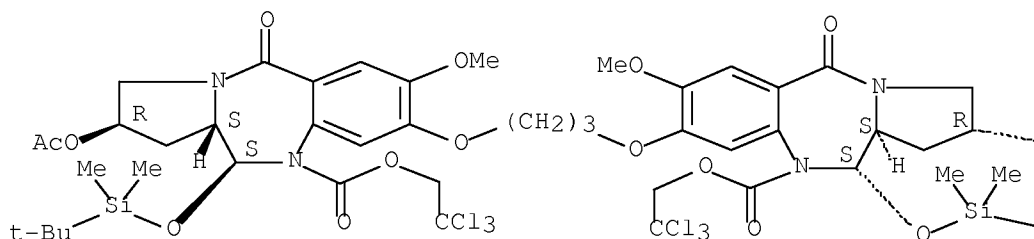
RN 864755-09-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2-(acetyloxy)-11-[[1,1-  
dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-,  
bis(2,2,2-trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA  
INDEX NAME)



Absolute stereochemistry.

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PAGE 1-B

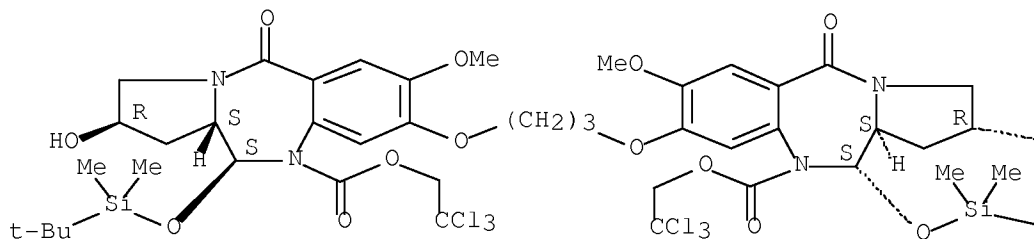
--- OAc

--- Bu-t

RN 864755-10-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]oxy]  
 y]-2,3,11,11a-tetrahydro-2-hydroxy-7-methoxy-5-oxo-, bis(2,2,2-  
 trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
 NAME)

Absolute stereochemistry.

PAGE 1-A



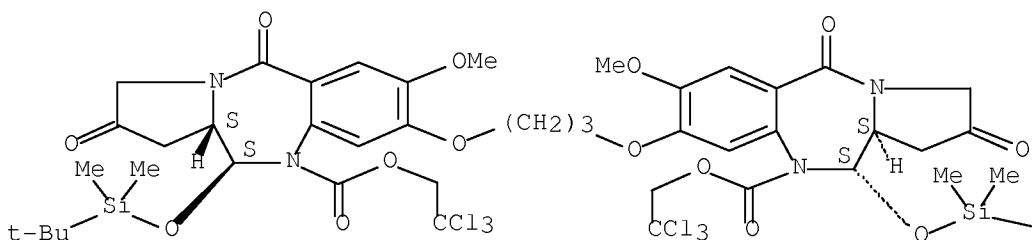
---OH

---Bu-t

RN 864755-11-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]oxy]  
-2,3,11,11a-tetrahydro-7-methoxy-2,5-dioxo-, bis(2,2,2-trichloroethyl)  
ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



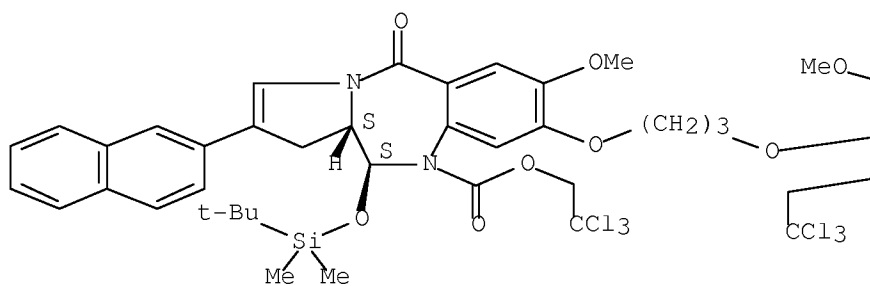
---Bu-t

RN 913262-19-8 CAPLUS

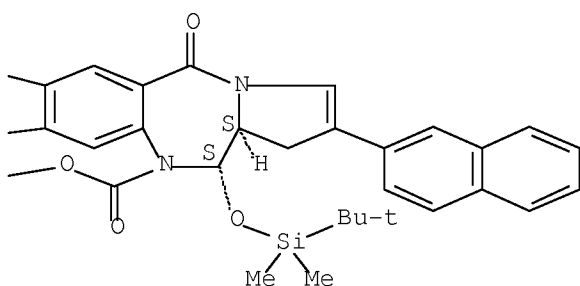
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]oxy]  
-11,11a-dihydro-7-methoxy-2-(2-naphthalenyl)-5-oxo-,  
bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
NAME)

Absolute stereochemistry.

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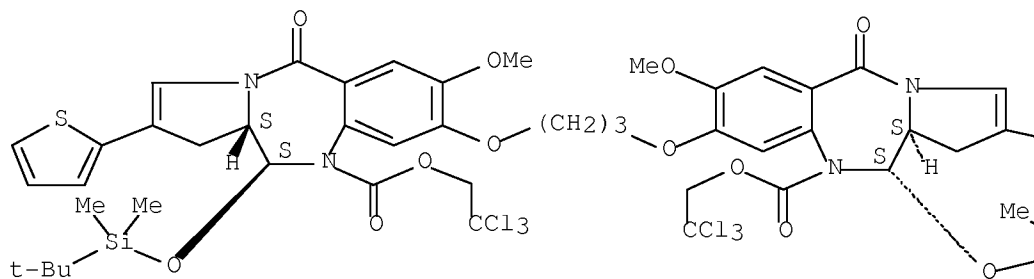
PAGE 1-B

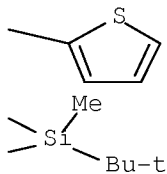


RN 913262-21-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[[(1,1-dimethylethyl)dimethylsilyl]ox  
 y]-11,11a-dihydro-7-methoxy-5-oxo-2-(2-thienyl)-, bis(2,2,2-  
 trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

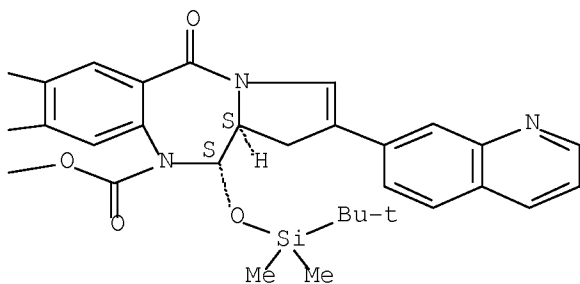
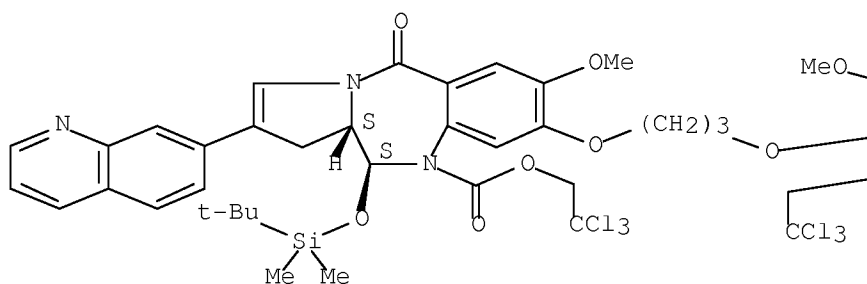




RN 913262-23-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]oxy]  
-11,11a-dihydro-7-methoxy-5-oxo-2-(7-quinoliny)-, bis(2,2,2-  
trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



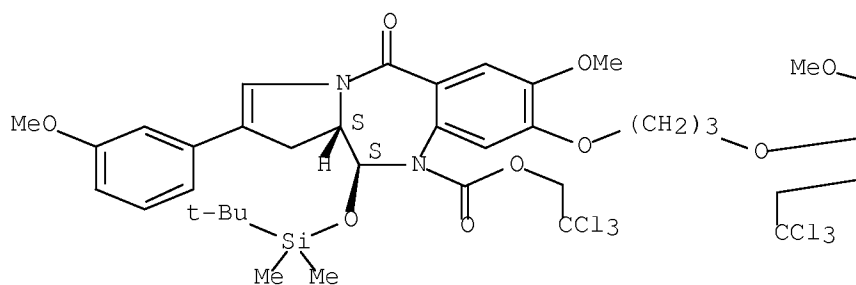
RN 913262-24-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]oxy]  
-11,11a-dihydro-7-methoxy-2-(3-methoxyphenyl)-5-oxo-,  
bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX

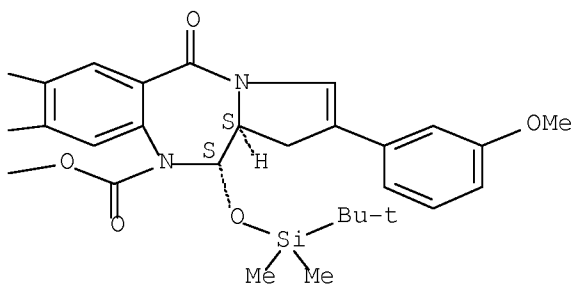
NAME)

Absolute stereochemistry.

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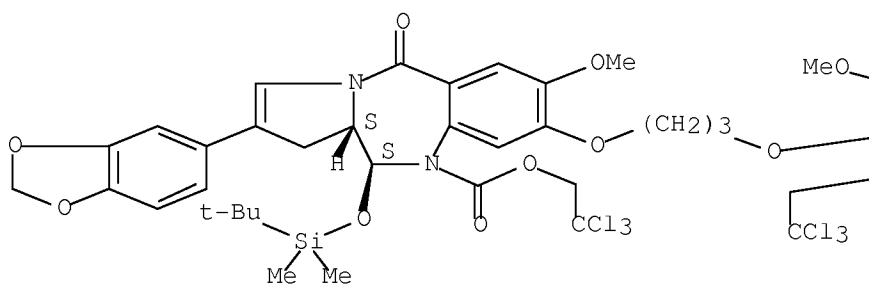
PAGE 1-B

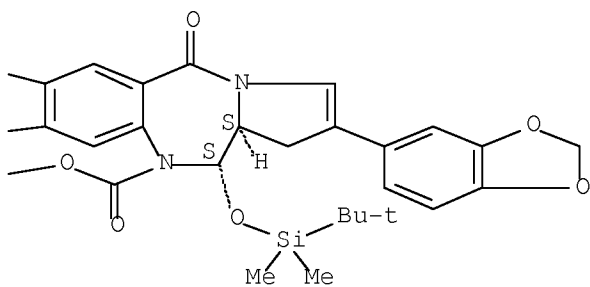


RN 913262-26-7 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2-(1,3-benzodioxol-5-yl)-11-[[ (1,1-  
dimethylethyl)dimethylsilyl]oxy]-11,11a-dihydro-7-methoxy-5-oxo-,  
bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
NAME)

Absolute stereochemistry.

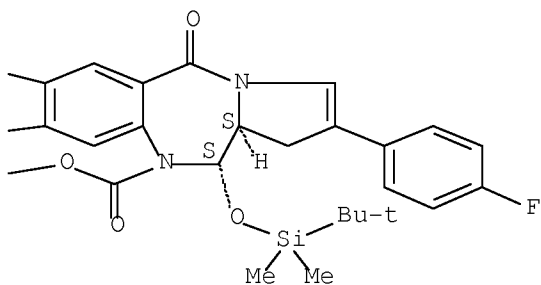
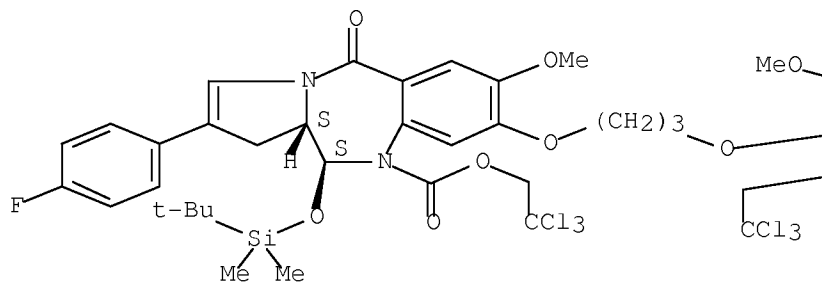
PAGE 1-A





RN 913262-28-9 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[ (1,1-dimethylethyl)dimethylsilyl]ox  
 y]-2-(4-fluorophenyl)-11,11a-dihydro-7-methoxy-5-oxo-,  
 bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
 NAME)

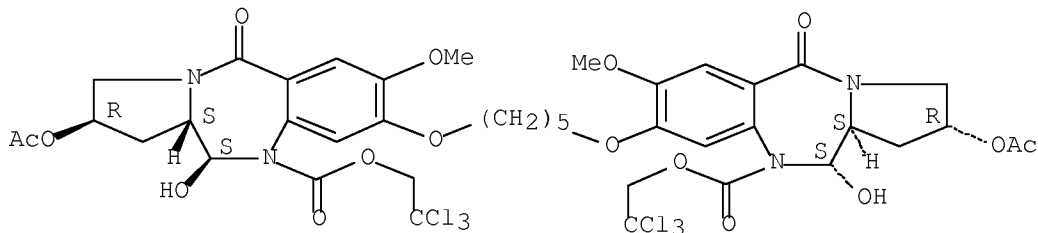
Absolute stereochemistry.



RN 913262-34-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,5-pentanediy]bis(oxy)]bis[2-(acetyloxy)-2,3,11,11a-tetrahydro-11-  
hydroxy-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester,  
(2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

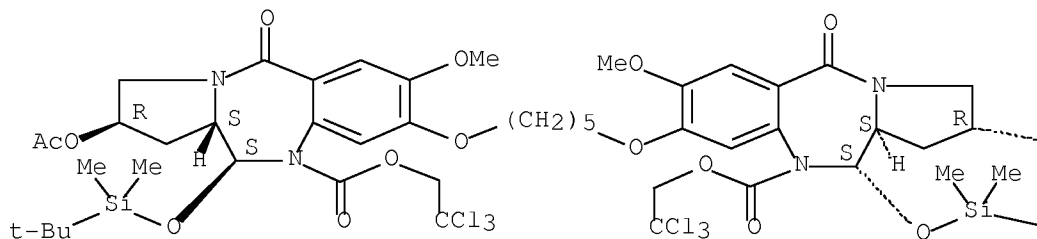


RN 913262-35-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,5-pentanediy]bis(oxy)]bis[2-(acetyloxy)-11-[[1,1-  
dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-,  
bis(2,2,2-trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA  
INDEX NAME)

Absolute stereochemistry.

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.....OAc

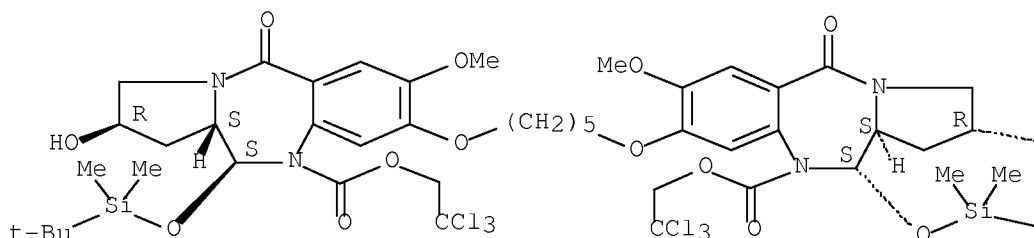
———Bu-t

RN 913262-36-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,5-pentanediy]bis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]ox  
y]-2,3,11,11a-tetrahydro-2-hydroxy-7-methoxy-5-oxo-, bis(2,2,2-  
trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
NAME)

Absolute stereochemistry.

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PAGE 1-B

OH

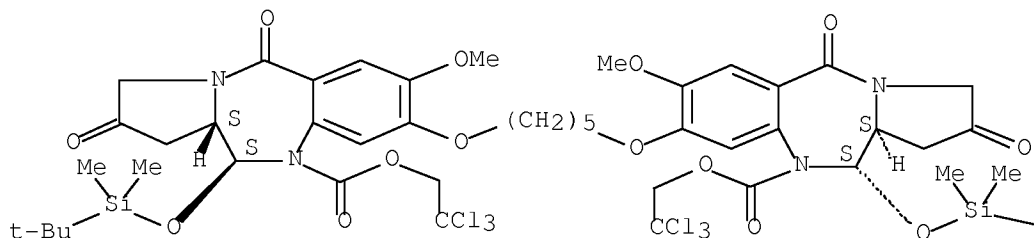
Bu-t

RN 913262-37-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,5-pentanediy]bis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]ox  
y]-2,3,11,11a-tetrahydro-2-hydroxy-7-methoxy-2,5-dioxo-,  
bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
NAME)

Absolute stereochemistry.

PAGE 1-A

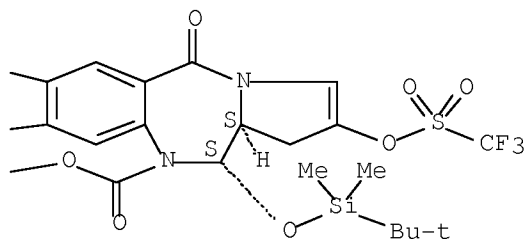
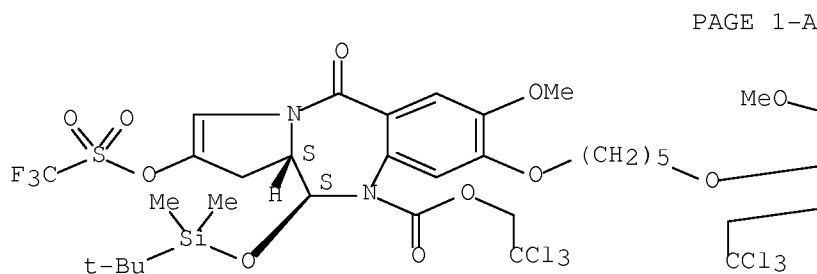




— Bu-t

RN	913262-38-1	CAPLUS
CN	1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediy]bis(oxy)]bis[11-[[[(1,1-dimethylethyl)dimethylsilyl]ox y]-11,11a-dihydro-7-methoxy-5-oxo-2-[[[(trifluoromethyl)sulfonyl]oxy]-, bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)	

Absolute stereochemistry.

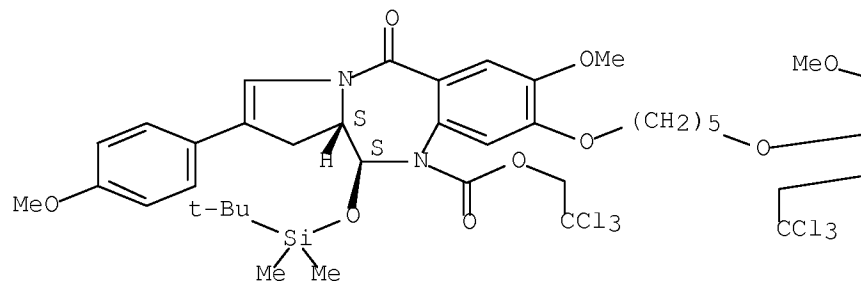


RN 913262-39-2 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,5-pentanediy]bis(oxy)]bis[[11-[[[1,1-dimethylethyl]dimethylsilyl]ox

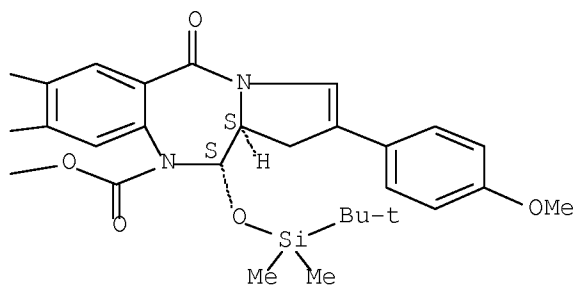
y]-11,11a-dihydro-7-methoxy-2-(4-methoxyphenyl)-5-oxo-,  
bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
NAME)

Absolute stereochemistry.

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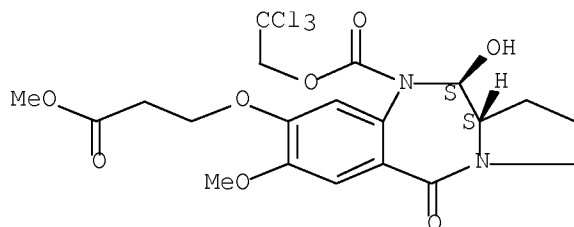
PAGE 1-B



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2006:1001150 CAPLUS Full-text  
 DN 146:220  
 TI DNA interstrand crosslinking agents: Synthesis, DNA interactions, and cytotoxicity of dimeric achiral seco-amino-CBI and conjugates of achiral seco-amino-CBI with pyrrolobenzodiazepine (PBD)  
 AU Purnell, Bethany; Sato, Atsushi; O'Kelley, Amanda; Price, Carly; Summerville, Kaitlin; Hudson, Stephen; O'Hare, Caroline; Kiakos, Konstantinos; Asao, Tetsuji; Lee, Moses; Hartley, John A.  
 CS Department of Chemistry, Furman University, Greenville, SC, 29613, USA  
 SO Bioorganic & Medicinal Chemistry Letters (2006), 16(21), 5677-5681  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Ltd.  
 DT Journal  
 LA English  
 OS CASREACT 146:220  
 AB The design and synthesis of three novel bisalkylating agents derived from the achiral seco-duocarmycin or CC-1065 analogs and pyrrolobenzodiazepines (PBDs) are described: achiral seco-CBI (cyclopropanebenz[e]indoline)-PBD 1, achiral seco-CI-PBD 2, and achiral seco-CBI dimer 3. Compds. 1 and 2 demonstrated enhanced cytotoxicity over the monomer counterparts against the growth of P815 murine mastocytoma cells in culture. Conjugate 1 was found to covalently react with adenine-N3 positions within the minor groove at AT-rich sequences and to produce DNA interstrand crosslinks. Both compds. were found to induce apoptosis in P815 cells. Due to its poor water solubility, dimer 3 did not give any appreciable DNA binding or cytotoxicity.  
 IT 219562-65-9  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (synthesis, DNA interactions, and cytotoxicity DNA interstrand crosslinking agents derived from the achiral seco-duocarmycin or CC-1065 analogs and pyrrolobenzodiazepines)  
 RN 219562-65-9 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(3-methoxy-3-oxopropoxy)-5-oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

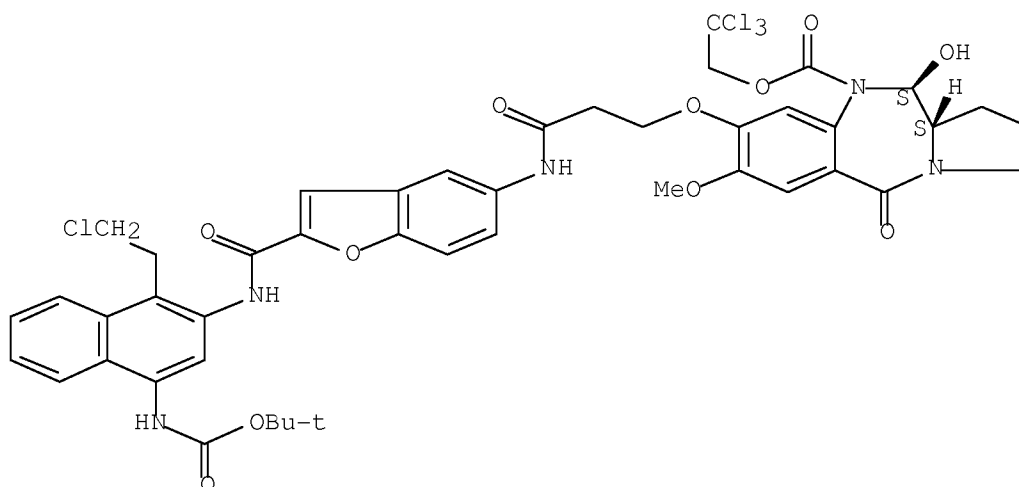
Absolute stereochemistry. Rotation (+).



IT 914774-46-2P 914774-47-3P 926622-02-8P  
 926622-03-9P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (synthesis, DNA interactions, and cytotoxicity DNA interstrand crosslinking agents derived from the achiral seco-duocarmycin or CC-1065 analogs and pyrrolobenzodiazepines)  
 RN 914774-46-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,

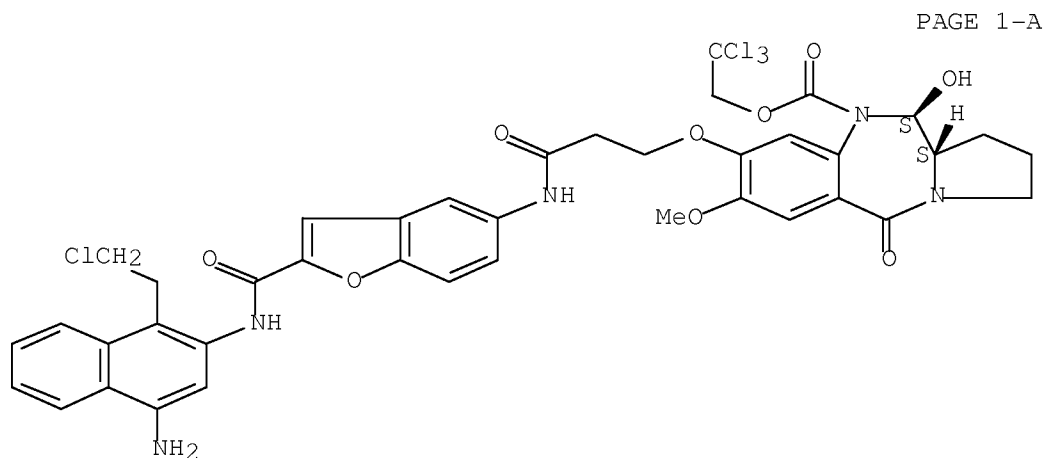
8-[3-[[2-[[[1-(2-chloroethyl)-4-[[ (1,1-dimethylethoxy)carbonyl]amino]-2-naphthalenyl]amino]carbonyl]-5-benzofuranyl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-5-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



RN 914774-47-3 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-[3-[[2-[[[4-amino-1-(2-chloroethyl)-2-naphthalenyl]amino]carbonyl]-5-benzofuranyl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, hydrochloride (1:1),  
 (11S,11aS)- (CA INDEX NAME)

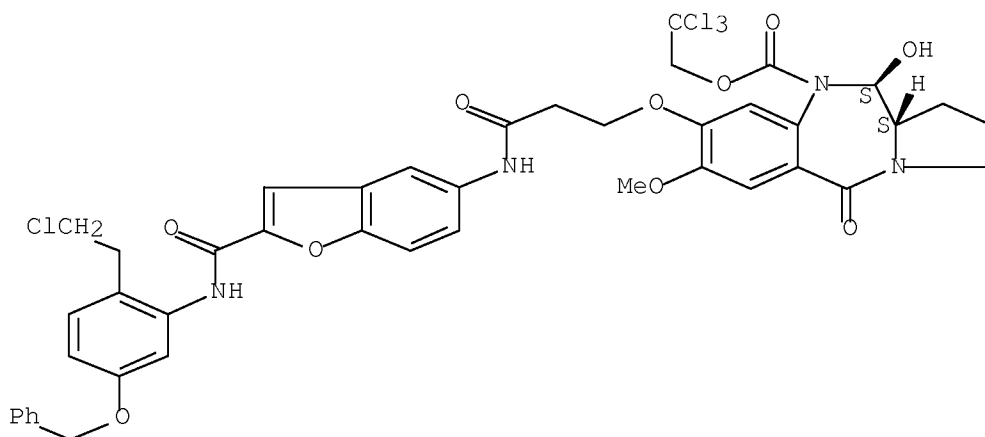
Absolute stereochemistry.



● HCl

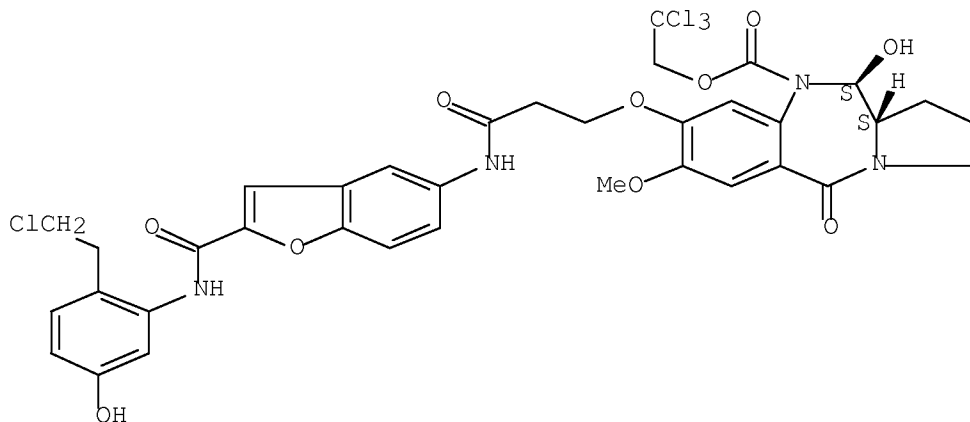
RN 926622-02-8 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-[3-[[2-[[[2-(2-chloroethyl)-5-(phenylmethoxy)phenyl]amino]carbonyl]-5-  
 benzofuranyl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-  
 methoxy-5-oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



RN 926622-03-9 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-[3-[[2-[[[2-(2-chloroethyl)-5-hydroxyphenyl]amino]carbonyl]-5-  
 benzofuranyl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-  
 methoxy-5-oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

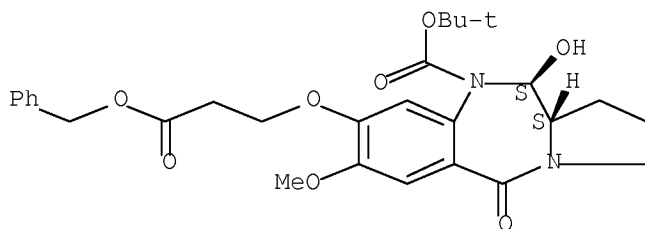
Absolute stereochemistry.



RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2006:782707 CAPLUS Full-text  
 DN 145:305639  
 TI Design, Synthesis, and Biophysical and Biological Evaluation of a Series  
 of Pyrrolobenzodiazepine-Poly(N-methylpyrrole) Conjugates  
 AU Wells, Geoff; Martin, Christopher R. H.; Howard, Philip W.; Sands, Zara  
 A.; Laughton, Charles A.; Tiberghien, Arnaud; Woo, Chi Kit; Masterson,  
 Luke A.; Stephenson, Marissa J.; Hartley, John A.; Jenkins, Terence C.;  
 Shnyder, Steven D.; Loadman, Paul M.; Waring, Michael J.; Thurston, David  
 E.  
 CS Cancer Research UK Gene Targeted Drug Design Research Group, The School of  
 Pharmacy, University of London, London, WC1N 1AX, UK  
 SO Journal of Medicinal Chemistry (2006), 49(18), 5442-5461  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 145:305639  
 AB A novel series of six Me ester-terminated C8-linked pyrrolobenzodiazepine  
 (PBD)-poly(N-methylpyrrole) conjugates has been synthesized and their DNA  
 interaction evaluated by thermal denaturation, DNA footprinting, and in vitro  
 transcription stop assays. The synergistic effect of attaching a PBD unit to  
 a polypyrrole fragment is illustrated by the large increase in DNA binding  
 affinity (up to 50-fold) compared to the individual PBD and pyrrole  
 components. The conjugates were found to bind mainly to identical DNA  
 sequences but with apparent binding site widths increasing with mol. length  
 and the majority of sites conforming to the consensus motif 5'-XGXWz (z = 3±1;  
 W = A or T; X = any base but preferably a purine). They also provided robust  
 sequence-selective blockade of transcription at sites corresponding approx. to  
 their DNA footprints. The conjugates were shown to have good cellular/nuclear  
 penetration properties, and a degree of correlation between cytotoxicity and  
 DNA-binding affinity was observed  
 IT 679005-40-4P 679005-41-5P 864672-71-9P  
 864672-72-0P 864672-97-9P 909415-12-9P  
 909415-20-9P 909415-21-0P 909415-22-1P  
 909415-23-2P 909415-24-3P 909415-25-4P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (design, synthesis, and biophys. and biol. evaluation of a series of  
 pyrrolobenzodiazepine-poly(N-methylpyrrole) conjugates)  
 RN 679005-40-4 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(  
 phenylmethoxy)propoxy]-, 1,1-dimethylethyl ester, (11S,11aS)- (CA INDEX  
 NAME)

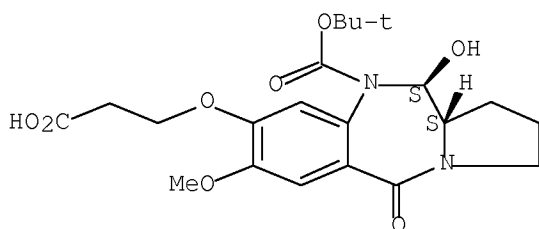
Absolute stereochemistry. Rotation (+).



RN 679005-41-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
10-(1,1-dimethylethyl) ester, (11S,11aS)- (CA INDEX NAME)

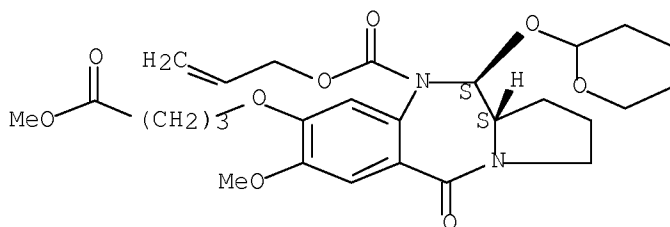
Absolute stereochemistry. Rotation (+).



RN 864672-71-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-8-(4-methoxy-4-oxobutoxy)-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA  
INDEX NAME)

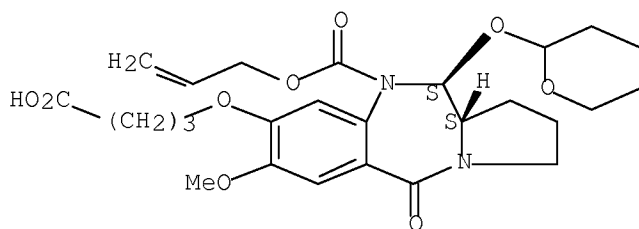
Absolute stereochemistry.



RN 864672-72-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(3-carboxypropoxy)-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-  
2H-pyran-2-yl)oxy]-, 10-(2-propen-1-yl) ester, (11S,11aS)- (CA INDEX  
NAME)

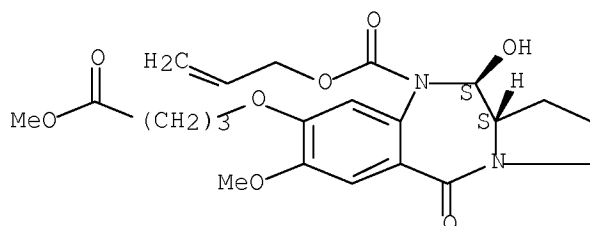
Absolute stereochemistry.



RN 864672-97-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(4-methoxy-4-oxobutoxy)-5-oxo-  
, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

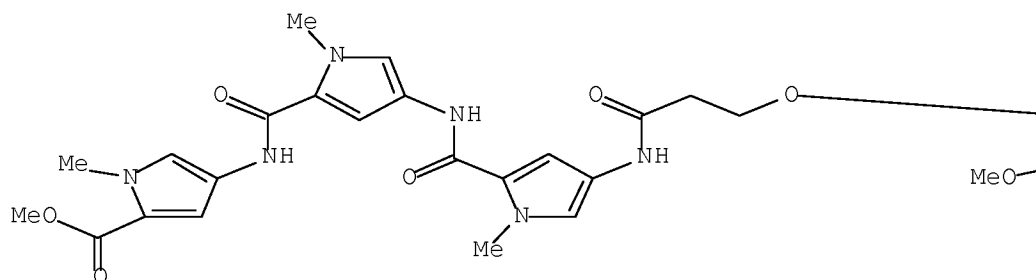


RN 909415-12-9 CAPLUS

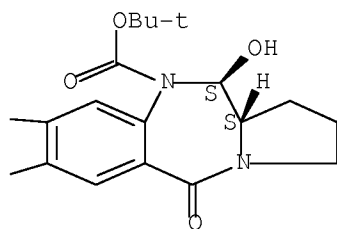
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-[3-[[5-[[[5-[[[5-(methoxycarbonyl)-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-3-oxopropoxy]-5-oxo-, 1,1-dimethylethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

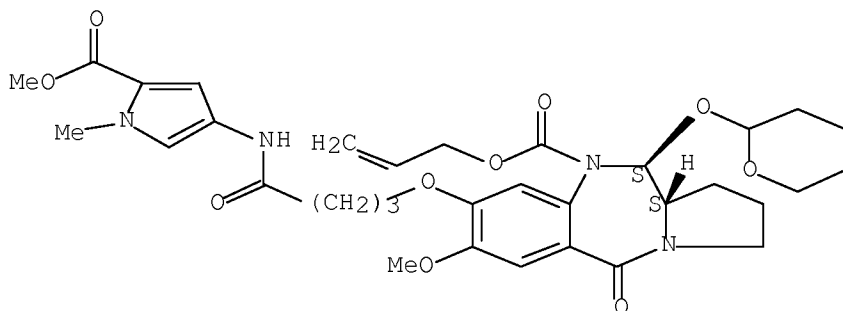




RN 909415-20-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[5-(methoxycarbonyl)-1-methyl-1H-  
pyrrol-3-yl]amino]-4-oxobutoxy]-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-,  
2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

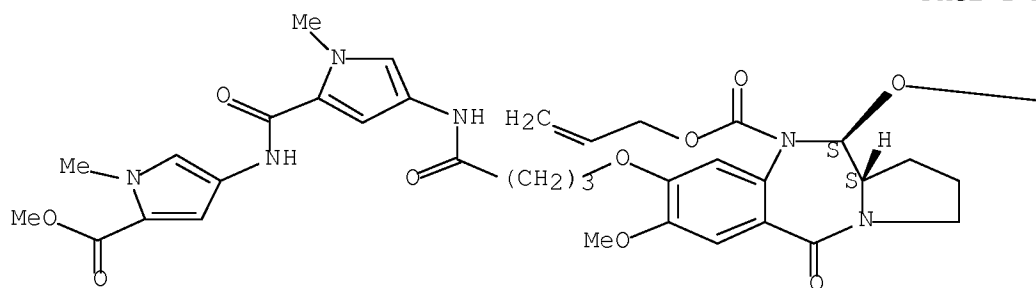
Absolute stereochemistry.



RN 909415-21-0 CAPLUS

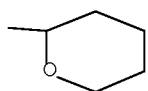
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[5-[[[5-(methoxycarbonyl)-1-methyl-  
1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-4-oxobutoxy]-  
5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester,  
(11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



PAGE 1-A

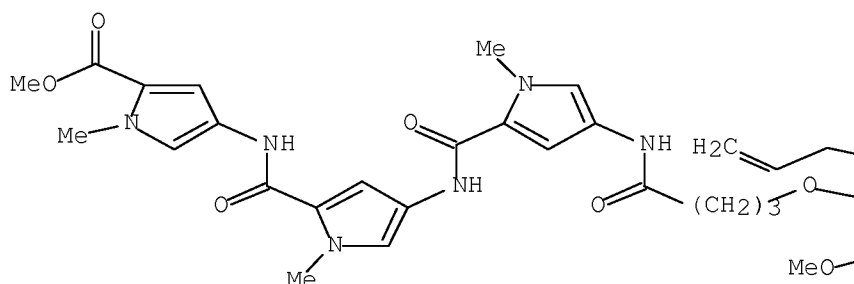
PAGE 1-B



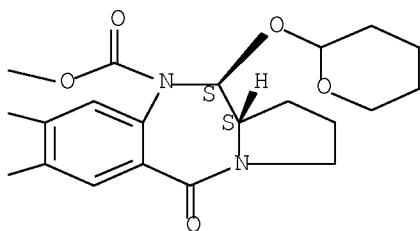
RN 909415-22-1 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[5-[[[5-[[[5-(methoxycarbonyl)-1-  
 methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-  
 yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-4-oxobutoxy]-5-oxo-11-  
 [(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA  
 INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

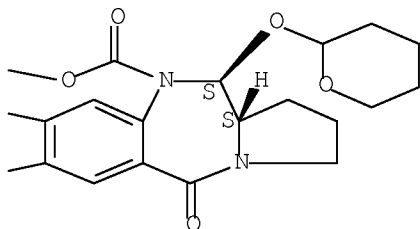
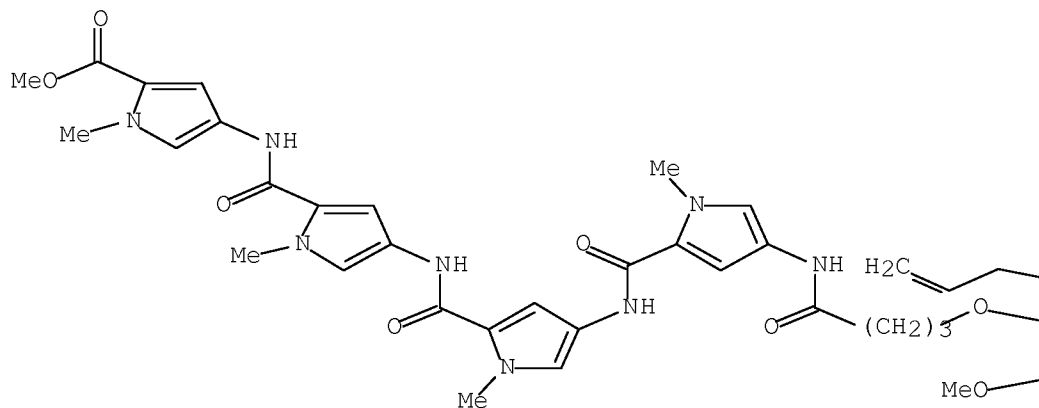


PAGE 1-B



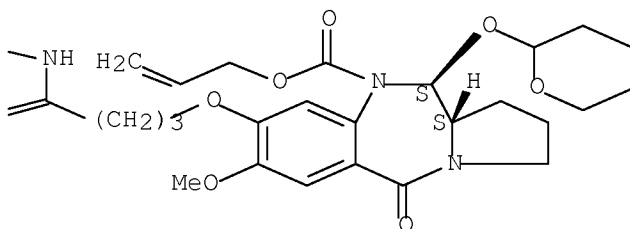
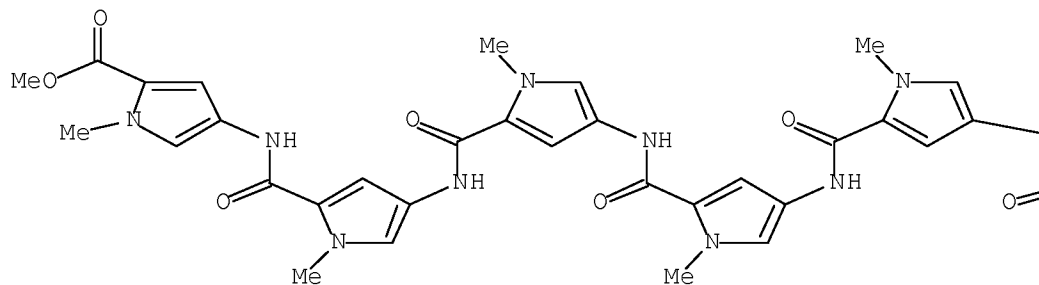
RN 909415-23-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[5-[[[5-[[[5-(methoxycarbonyl)-  
 1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-  
 yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-  
 pyrrol-3-yl]amino]-4-oxobutoxy]-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-,  
 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



RN 909415-24-3 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[[5-[[[5-[[[5-[[[5-[[[5-  
 (methoxycarbonyl)-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-  
 pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-  
 methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-4-  
 oxobutoxy]-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester,  
 (11S,11aS)- (CA INDEX NAME)

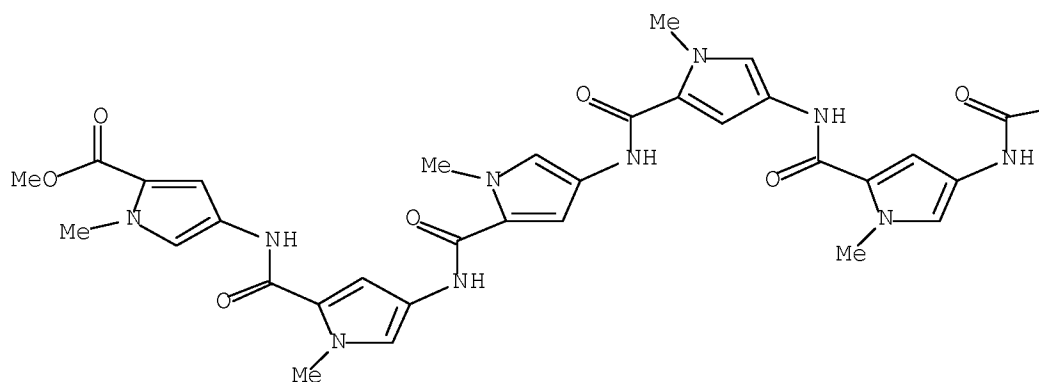
Absolute stereochemistry.

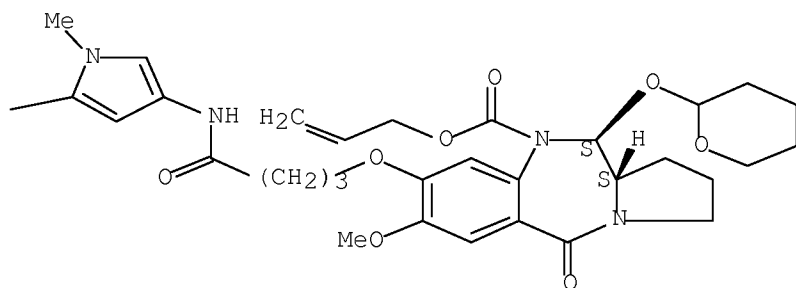


RN 909415-25-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-8-[4-[[[5-[[[5-[[[5-[[[5-[[[5-  
(methoxycarbonyl)-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-  
pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-  
methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-  
yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-4-oxobutoxy]-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA  
INDEX NAME)

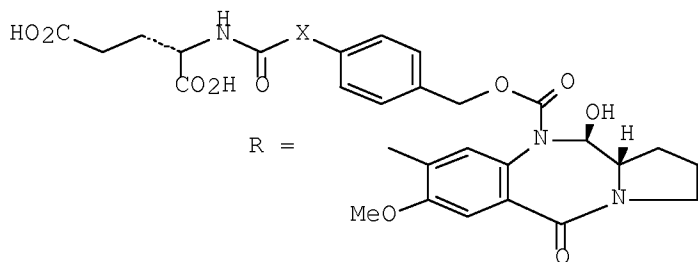
Absolute stereochemistry.





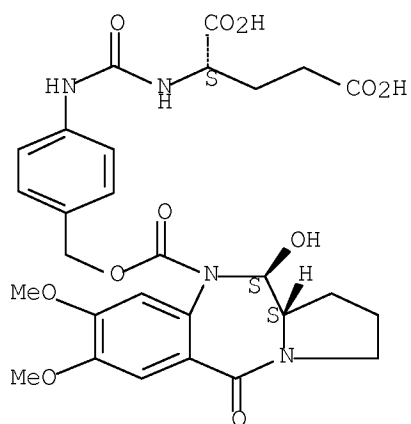
RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:1251578 CAPLUS Full-text  
 DN 144:150340  
 TI Synthesis and biological evaluation of novel pyrrolo[2,1-  
 c][1,4]benzodiazepine prodrugs for use in antibody-directed enzyme prodrug  
 therapy  
 AU Masterson, Luke A.; Spanswick, Victoria J.; Hartley, John A.; Begent,  
 Richard H.; Howard, Philip W.; Thurston, David E.  
 CS CR-UK Gene Targeting Drug Design Research Group, School of Pharmacy,  
 University of London, London, WC1 1AX, UK  
 SO Bioorganic & Medicinal Chemistry Letters (2006), 16(2), 252-256  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier B.V.  
 DT Journal  
 LA English  
 OS CASREACT 144:150340  
 GI



AB The design, synthesis and evaluation of four novel pyrrolo[2,1-  
 c][1,4]benzodiazepine (PBD) prodrugs ROME and RO(CH<sub>2</sub>)<sub>3</sub>OR [X = O, NH] for  
 potential use in carboxypeptidase G2 (CPG2)-based antibody-directed enzyme  
 prodrug therapy (ADEPT) is reported. Although all four prodrugs were shown to  
 be less cytotoxic than the released parent PBDs, the urea prodrugs were found  
 to be too unstable for use in ADEPT, whereas the carbamates are both stable in  
 an aqueous environment and are good substrates for CPG2.  
 IT 848004-47-7F 848004-56-8F 848004-84-2P  
 848004-85-3F  
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic  
 preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant  
 or reagent)  
 (preparation and biol. evaluation of pyrrolo[2,1-c][1,4]benzodiazepine  
 prodrugs for use in antibody-directed enzyme prodrug therapy)  
 RN 848004-47-7 CAPLUS  
 CN L-Glutamic acid, N-[[[4-[[[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-  
 7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-  
 yl]carbonyl]oxy]methyl]phenyl]amino]carbonyl]- (CA INDEX NAME)

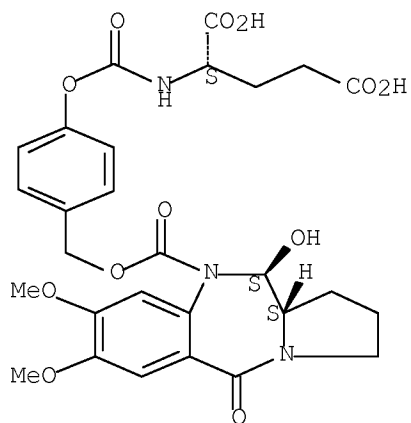
Absolute stereochemistry. Rotation (+).



RN 848004-56-8 CAPLUS

CN L-Glutamic acid, N-[[4-[[[[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-yl]carbonyl]oxy]methyl]phenoxy]carbonyl]- (CA INDEX NAME)

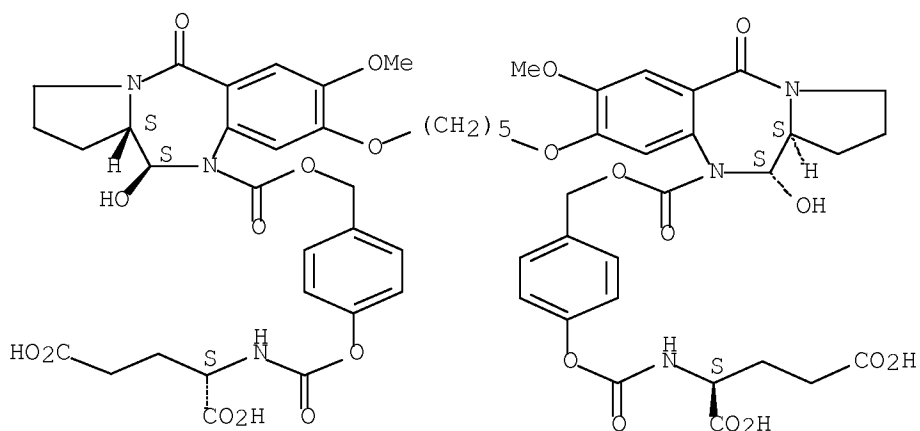
Absolute stereochemistry.



RN 848004-84-2 CAPLUS

CN L-Glutamic acid, N,N'-[1,5-pentanediy]bis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneoxycarbonyl]]bis- (9CI)  
(CA INDEX NAME)

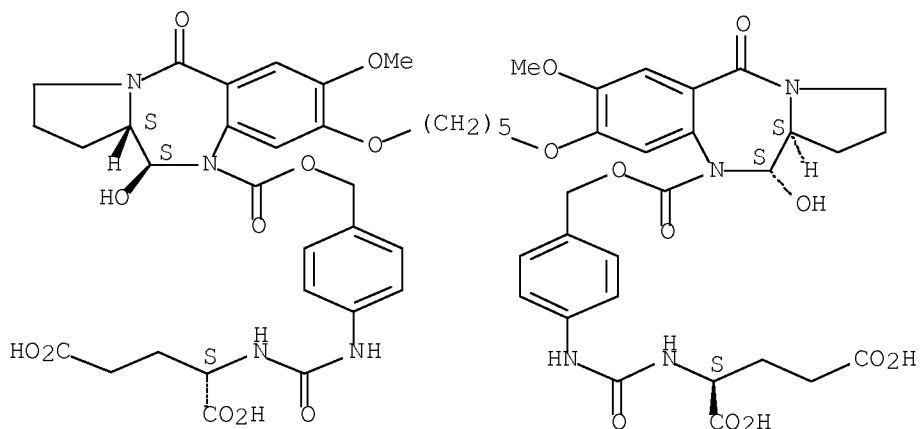
Absolute stereochemistry. Rotation (+).



RN 848004-85-3 CAPLUS

CN L-Glutamic acid, N,N'-[1,5-pentanediyldis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneiminocarbonyl]]bis- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



L11 ANSWER 7 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:1004755 CAPLUS Full-text

DN 143:306350

TI Preparation, DNA crosslinking reactivity, antitumor and antibacterial activity of pyrrolobenzodiazepine dimers

IN Howard, Philip Wilson; Gregson, Stephen John; Taylor, Peter William; Thurston, David Edwin; Hadjivassileva, Tsveta Stepanova

PA Spirogen Limited, UK

SO PCT Int. Appl., 62 pp.

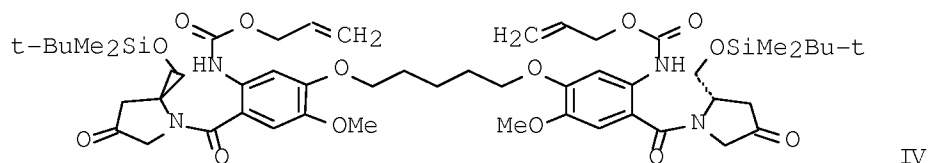
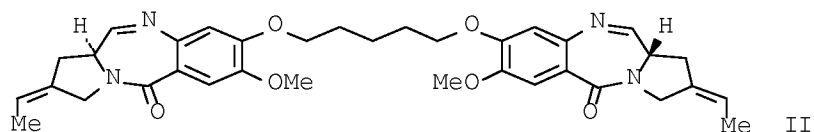
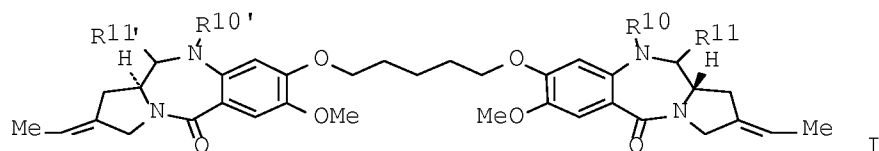
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

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PI	WO 2005085260	A1	20050915	WO 2005-GB915	20050309
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
	RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	EP 1723152	A1	20061122	EP 2005-717979	20050309
	R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR			
	JP 2007528383	T	20071011	JP 2007-502398	20050309
	US 20070185073	A1	20070809	US 2007-598691	20070214
PRAI	GB 2004-5319	A	20040309		
	GB 2004-12409	A	20040603		
	WO 2005-GB915	W	20050309		
OS	CASREACT 143:306350; MARPAT 143:306350				
GI					



AB Title compds. I [R10 = N-protecting group; R11 = OH, OR12; R12 = O-protecting group; or R10 and R11 together form a double bond between N10 and C11; R10' = R10; R11' = R11; and their geometrical isomers, salts and solvates] were prepared for use in the manufacture of a medicament for treating gene-based diseases, such as proliferative, and infections by Gram-pos. bacteria. For example, Z-, Z- isomer of II (III) was prepared, in 4 steps, by Wittig reaction of bis-ketone IV with ethyltriphenylphosphonium bromide, tert-butyldimethylsilyl-deprotection, cyclization, and allyloxycarbonyl-deprotection. Pyrrolobenzodiazepine dimer III displayed antitumor potency (IC50 0.05 nM) against K562 human chronic myeloid leukemia cells and crosslinking reactivity (XL50 = 2.7±1.6 nM). Pyrrolobenzodiazepine dimer III showed activity against Gram-pos. bacteria; for example the MIC90 values for III were 0.03 against methicillin resistant Staphylococcus aureus, 0.06 mg/L against vancomycin resistant enterococci and Listeria monocytogenes, and 0.015 mg/L against Streptococcus pyogenes and Streptococcus agalactiae.

IT 864528-73-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

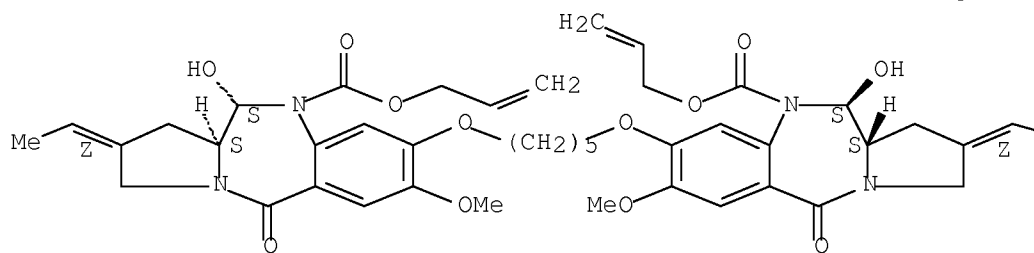
(intermediate; preparation of pyrrolobenzodiazepine dimers as antiproliferative and antibacterial agents)

RN 864528-73-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediy]bis(oxy)]bis[2-ethylidene-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, di-2-propenyl ester, (2Z,2'Z,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

— Me

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 8 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:1004754 CAPLUS Full-text  
 DN 143:306349  
 TI Preparation, DNA crosslinking reactivity and antiproliferative activity of  
 pyrrolobenzodiazepine dimers  
 IN Howard, Philip Wilson; Kang, Gyoung-Dong  
 PA Spirogen Limited, UK  
 SO PCT Int. Appl., 108 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005085259	A2	20050915	WO 2005-GB770	20050301
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	CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,				
	GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,				
	LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,				
	NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM,				
	SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW:				
	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,				
	AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,				
	EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,				
	RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,				
	MR, NE, SN, TD, TG				
EP	1723151	A2	20061122	EP 2005-717848	20050301
	R:				
	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,				
	IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
IN	2006DN04922	A	20070817	IN 2006-DN4922	20060825
US	20070191309	A1	20070816	US 2007-598482	20070206
PRAI	GB 2004-4577	A	20040301		
	WO 2005-GB770	W	20050301		
OS	CASREACT 143:306349; MARPAT 143:306349				
GI					

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Title compds. I [R2, R3 = independently H, :O, :CH2, CN, R, OR, halo, etc.;  
 R6, R9 = independently H, R, OH, OR, NRR', SH, etc.; R, R' = independently  
 (un)substituted alkyl, heterocyclyl, aryl; when X = RA, Y = OH or A-R''-A'-  
 PDB; when X = OH or A-R''-A'-PDB, Y = RA; RA = H, R, OR, NO2, etc.; A, A' =  
 independently O, S, NH; R'' = alkylene, optionally interrupted by one or more  
 O, S, NH and/or aryl rings; PDB = pyrrolobenzodiazepine; R10 = carbamate-based  
 N protecting group; R11 = O protecting group; or R10 and R11 together form a  
 double bond between N10 and C11; and their salts, solvates, and chemical  
 protected forms] were prepared for the manufacture of a medicament for  
 treating a proliferative disease. Thus, reacting pyrrolobenzodiazepine (PBD)  
 monomer II with 1,5-diiodopentane, followed by deprotection/dehydration gave  
 PBD dimer III. PBD dimer III displayed antitumor potency (IC50 = 0.5 µM)  
 against K562 human chronic myeloid leukemia cells DNA crosslinking reactivity  
 (XL50 = 0.07 µM).

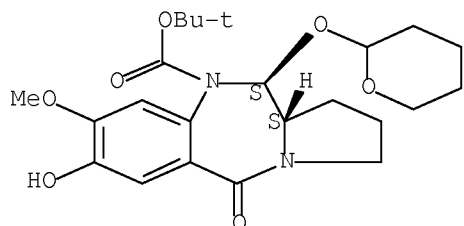
IT 864665-31-6P  
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic  
 preparation); THU (Therapeutic use); BIOL (Biological study); PREP  
 (Preparation); RACT (Reactant or reagent); USES (Uses)

(drug candidate; preparation, DNA crosslinking reactivity and cytotoxicity of pyrrolobenzodiazepines)

RN 864665-31-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-7-hydroxy-8-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 1,1-dimethylethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



IT 864665-57-6P 864665-75-8P 864665-77-0P

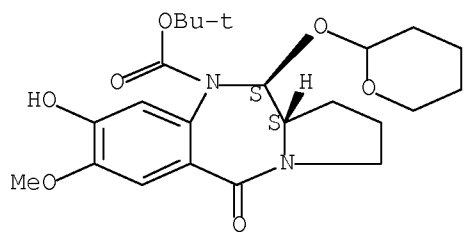
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation, DNA crosslinking reactivity and cytotoxicity of pyrrolobenzodiazepines)

RN 864665-57-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-8-hydroxy-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 1,1-dimethylethyl ester, (11S,11aS)- (CA INDEX NAME)

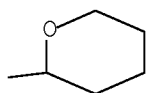
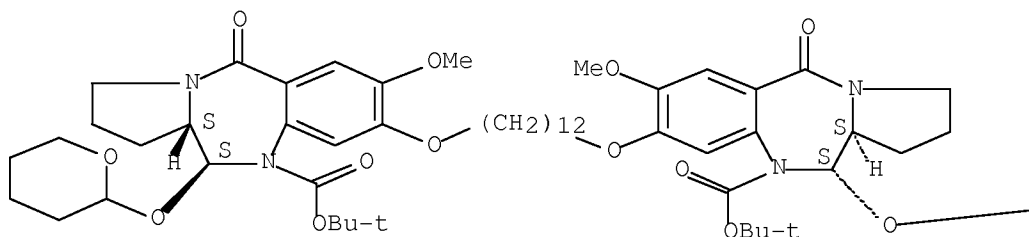
Absolute stereochemistry.



RN 864665-75-8 CAPLUS

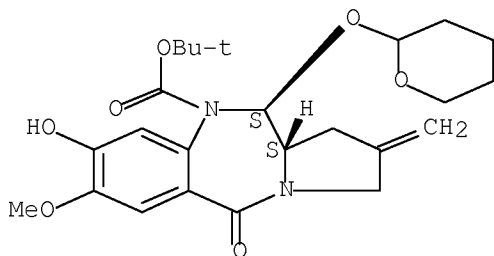
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,12-dodecanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 864665-77-0 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-8-hydroxy-7-methoxy-2-methylene-5-oxo-11-  
 [(tetrahydro-2H-pyran-2-yl)oxy]-, 1,1-dimethylethyl ester, (11S,11aS)-  
 (CA INDEX NAME)

Absolute stereochemistry.



IT 864665-35-0P, (+)-(11S,11aS)-7-Benzyloxy-10-(tert-  
 butyloxycarbonyl)-1-hydroxy-8-methoxy-1,2,3,10,11,11a-hexahydro-5H-  
 pyrrolo[2,1-c][1,4]benzodiazepin-5-one 864665-36-1P  
 864665-37-2P 864665-39-4P 864665-41-8P  
 864665-43-0P 864665-45-2P 864665-47-4P  
 864665-49-6P 864665-51-0P 864665-53-2P  
 864665-55-4P 864665-59-8P, (+)-(11S,11aS)-8-Benzyloxy-10-  
 (tert-butyloxycarbonyl)-1-hydroxy-7-methoxy-1,2,3,10,11,11a-hexahydro-5H-  
 pyrrolo[2,1-c][1,4]benzodiazepin-5-one 864665-60-1P  
 864665-61-2P 864665-62-3P 864665-63-4P  
 864665-64-5P 864665-65-6P 864665-67-8P

864665-69-0P 864665-71-4P 864665-73-6P

864665-81-6P, (+)-(1S,11aS)-8-Benzyloxy-10-(tert-butyloxycarbonyl)-1-hydroxy-7-methoxy-2-oxo-1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one 864665-82-7P, (+)-(11S,11aS)-10-(tert-Butyloxycarbonyl)-8,1-dihydroxy-7-methoxy-2-oxo-1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one 864665-83-8P

864665-84-9P 864665-85-0P 864665-87-2P

864665-89-4P

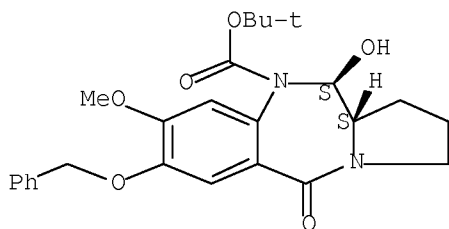
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation, DNA crosslinking reactivity and cytotoxicity of pyrrolobenzodiazepines)

RN 864665-35-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-8-methoxy-5-oxo-7-(phenylmethoxy)-, 1,1-dimethylethyl ester, (11S,11aS)- (CA INDEX NAME)

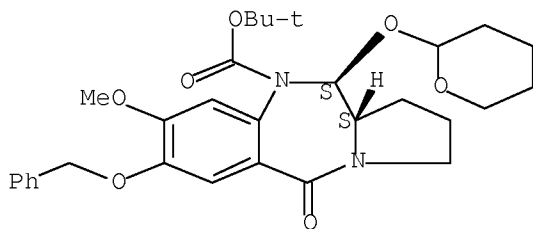
Absolute stereochemistry. Rotation (+).



RN 864665-36-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-8-methoxy-5-oxo-7-(phenylmethoxy)-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 1,1-dimethylethyl ester, (11S,11aS)- (CA INDEX NAME)

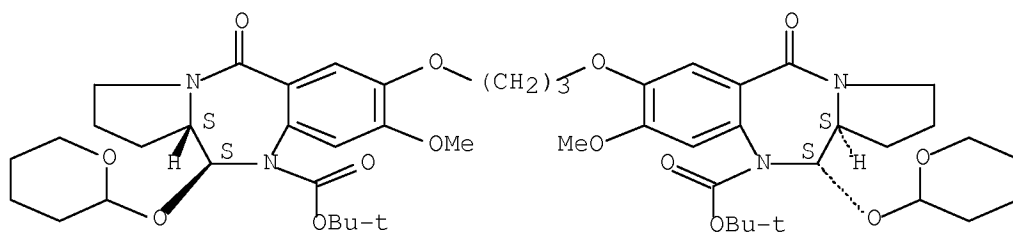
Absolute stereochemistry.



RN 864665-37-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 7,7'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

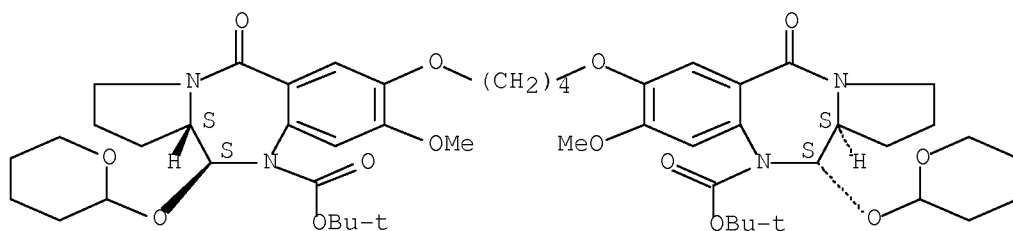
Absolute stereochemistry.



RN 864665-39-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,4-butanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

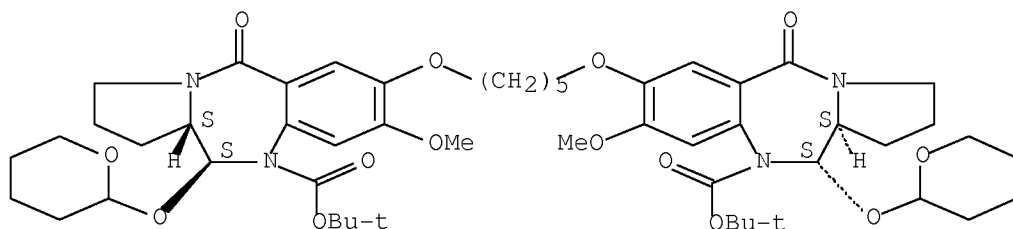
Absolute stereochemistry.



RN 864665-41-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,5-pentanedylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

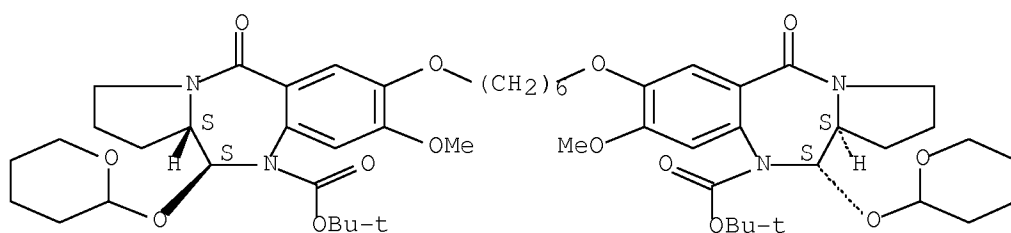
Absolute stereochemistry.



RN 864665-43-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,6-hexanedylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

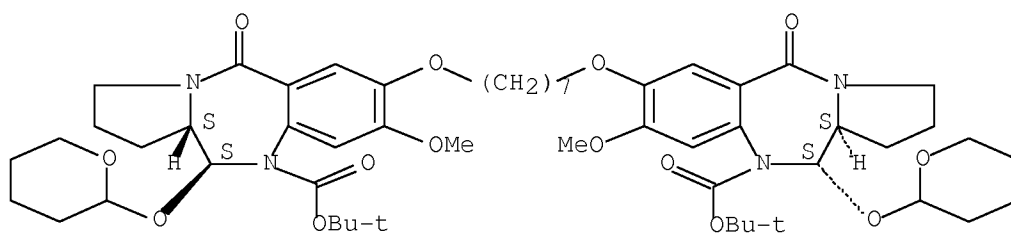
Absolute stereochemistry.



RN 864665-45-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,7-heptanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

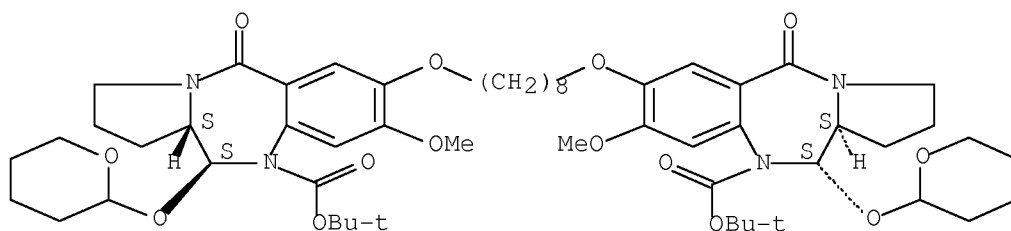
Absolute stereochemistry.



RN 864665-47-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,8-octanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



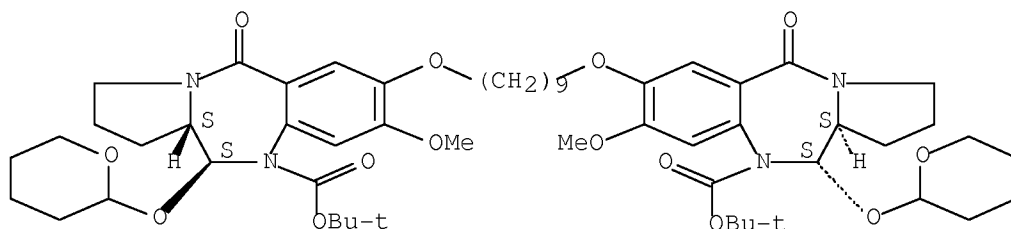
RN 864665-49-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,9-nonanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,



(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

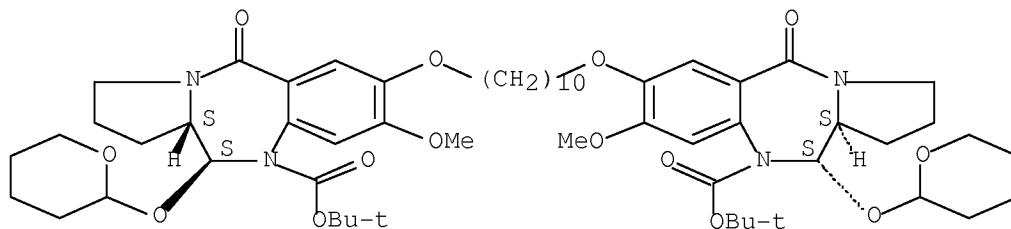
Absolute stereochemistry.



RN 864665-51-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,10-decanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

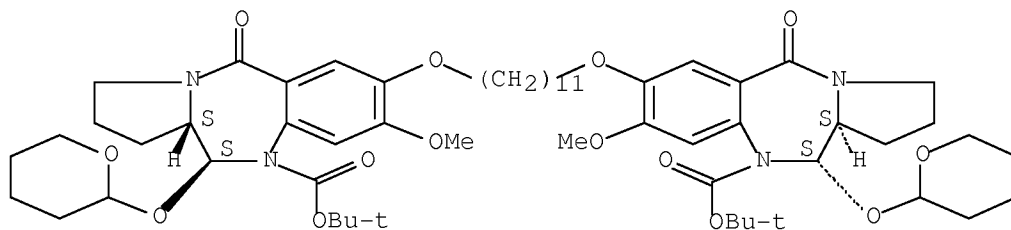
Absolute stereochemistry.



RN 864665-53-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,11-undecanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-  
11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

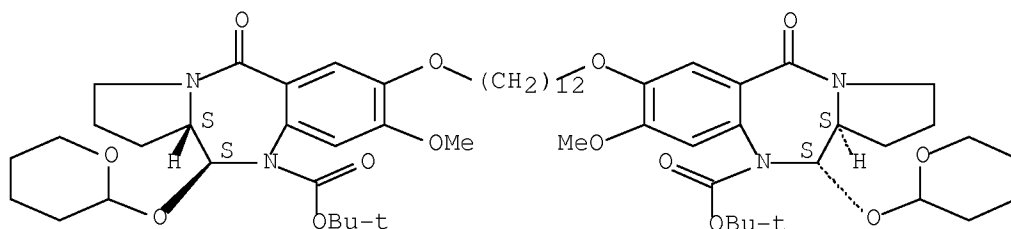


RN 864665-55-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,

7,7'-[1,12-dodecanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

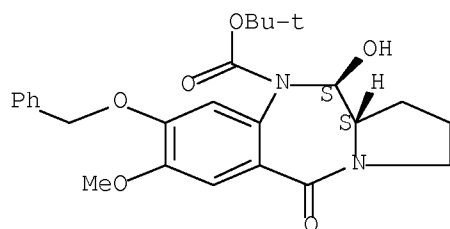
Absolute stereochemistry.



RN 864665-59-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-, 1,1-dimethylethyl ester, (11S,11aS)- (CA INDEX NAME)

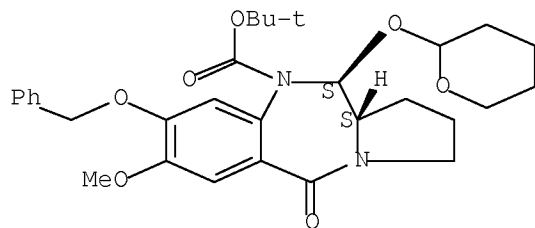
Absolute stereochemistry. Rotation (+).



RN 864665-60-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-7-methoxy-5-oxo-8-(phenylmethoxy)-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 1,1-dimethylethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



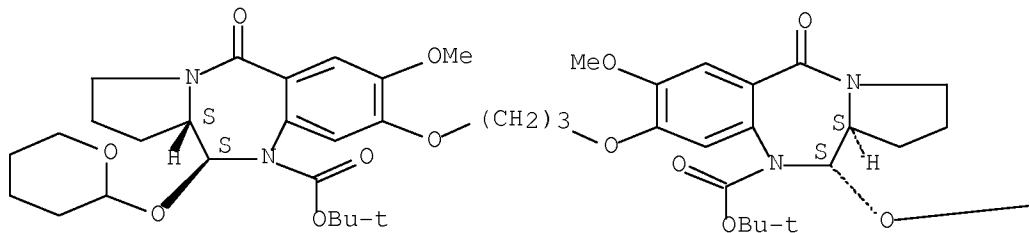
RN 864665-61-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,

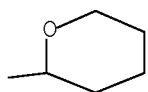
8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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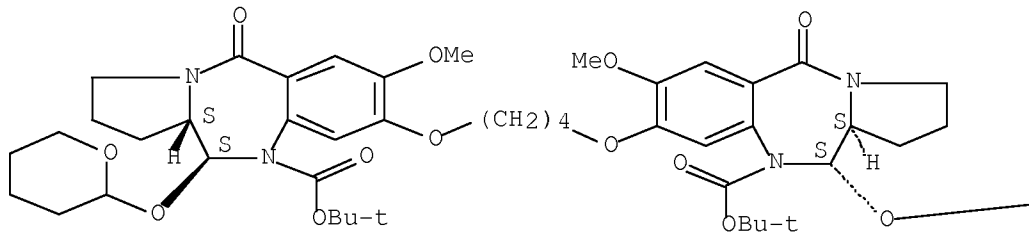
PAGE 1-B

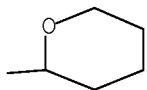


RN 864665-62-3 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,4-butanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

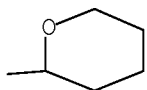
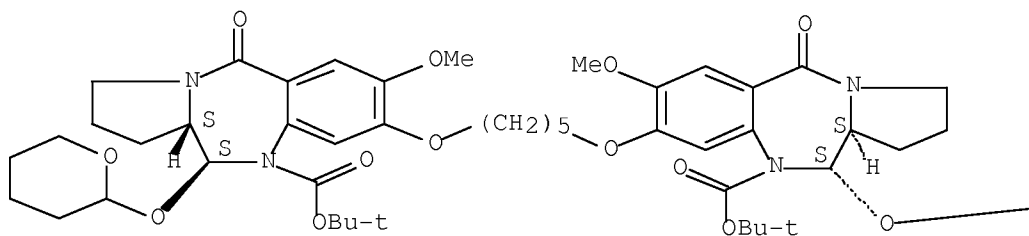
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RN 864665-63-4 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,5-pentanediylobis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
 [(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
 (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

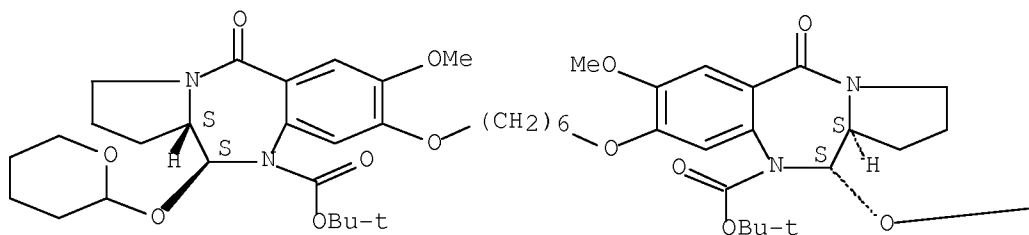
Absolute stereochemistry.



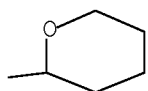
RN 864665-64-5 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,6-hexanediylobis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
 [(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
 (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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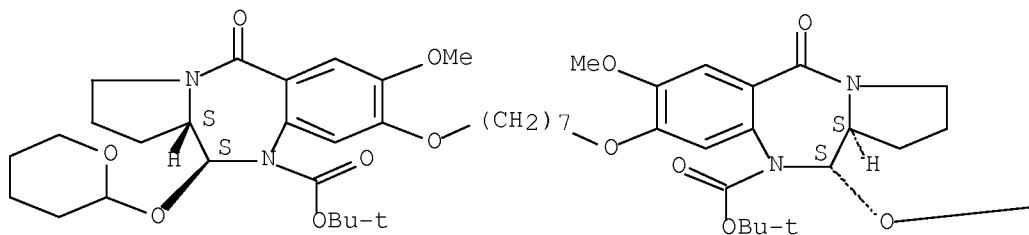
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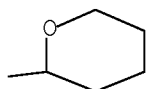
RN 864665-65-6 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,7-heptanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
 [(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
 (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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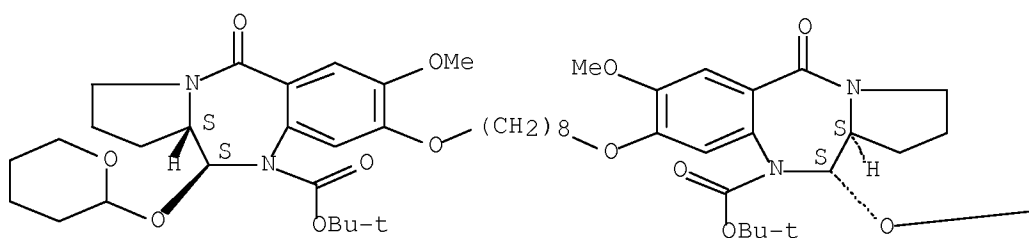
PAGE 1-B



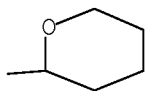
RN 864665-67-8 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,8-octanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
 [(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
 (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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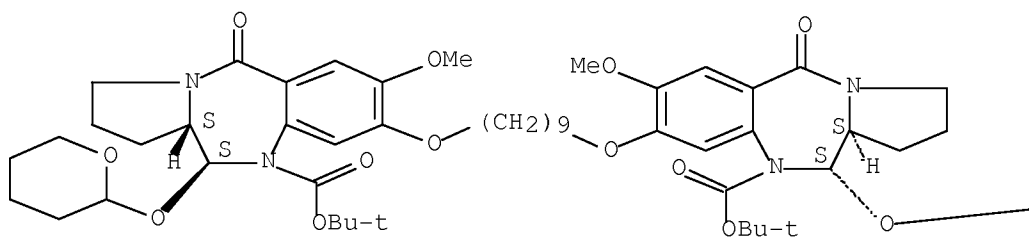
PAGE 1-B

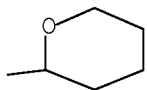


RN 864665-69-0 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,9-nonanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
 [(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
 (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

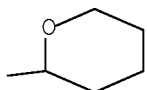
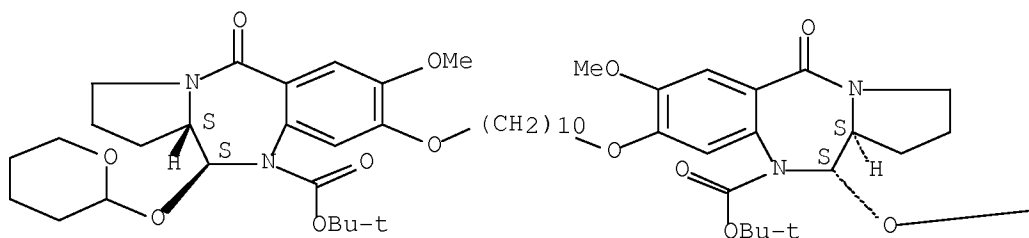
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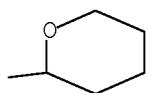
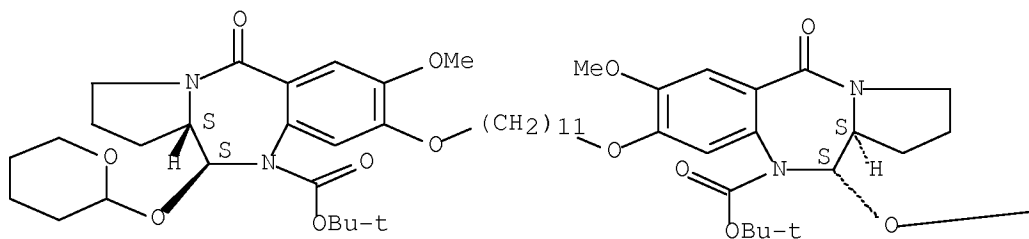
RN 864665-71-4 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,10-decanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
 [(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
 (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 864665-73-6 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,11-undecanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-  
 11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
 (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

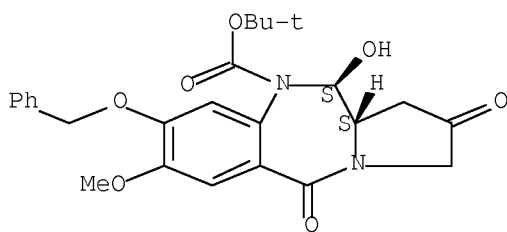
Absolute stereochemistry.



RN 864665-81-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2,5-dioxo-8-(phenylmethoxy)-,  
1,1-dimethylethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

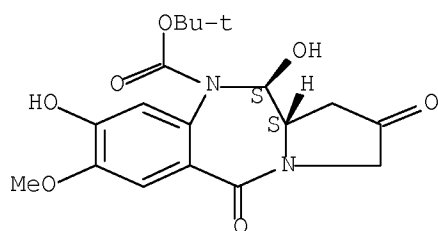


RN 864665-82-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-8,11-dihydroxy-7-methoxy-2,5-dioxo-  
1,1-dimethylethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

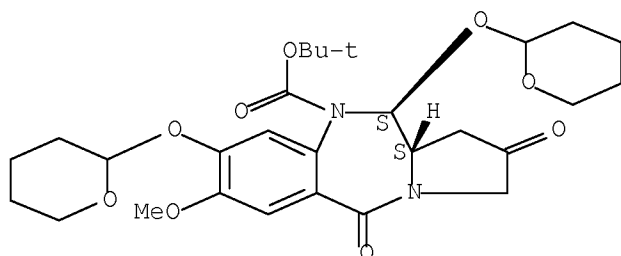




RN 864665-83-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-2,5-dioxo-8,11-bis[(tetrahydro-2H-pyran-2-yl)oxy]-, 1,1-dimethylethyl ester, (11S,11aS)- (CA INDEX NAME)

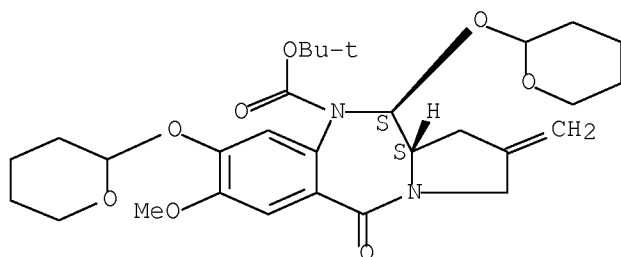
Absolute stereochemistry.



RN 864665-84-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-8,11-bis[(tetrahydro-2H-pyran-2-yl)oxy]-, 1,1-dimethylethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

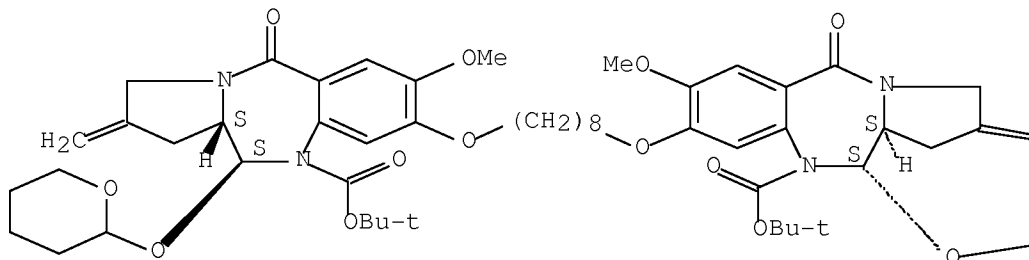


RN 864665-85-0 CAPLUS

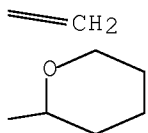
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,8-octanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



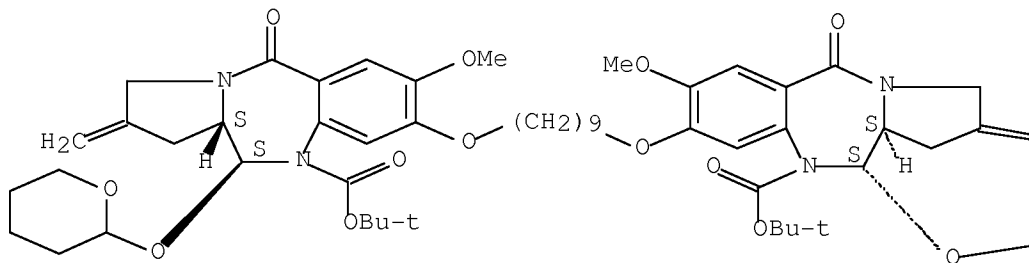
PAGE 1-B

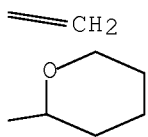


RN 864665-87-2 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,9-undecanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-2-  
methylene-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-  
dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

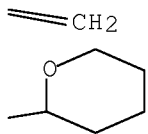
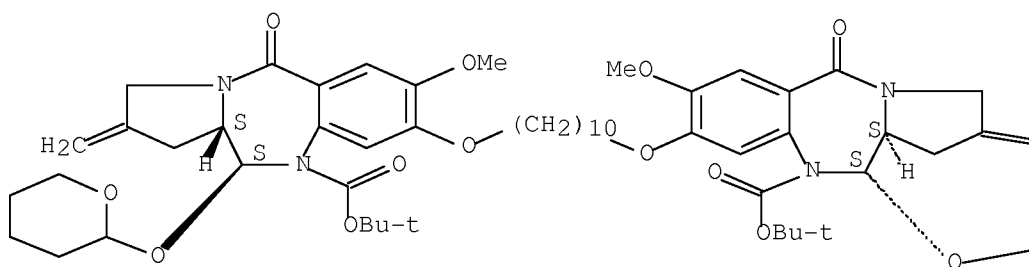




RN 864665-89-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,10-decanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 9 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:1004748 CAPLUS Full-text  
 DN 143:306348  
 TI Preparation of pyrrolobenzodiazepinone derivatives as antitumor agents  
 IN Howard, Philip Wilson; Gregson, Stephen John  
 PA Spirogen Limited, UK  
 SO PCT Int. Appl., 88 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005085251	A1	20050915	WO 2005-GB768	20050301
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
	RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	AU 2005219626	A1	20050915	AU 2005-219626	20050301
	CA 2558195	A1	20050915	CA 2005-2558195	20050301
	EP 1720881	A1	20061115	EP 2005-717846	20050301
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	JP 2007525535	T	20070906	JP 2007-501340	20050301
	US 20070173497	A1	20070726	US 2007-598518	20070206
PRAI	GB 2004-4575	A	20040301		
	GB 2004-26392	A	20041201		
	WO 2005-GB768	W	20050301		
OS	CASREACT 143:306348; MARPAT 143:306348				
GI					

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Title compds. I [R1 = labile leaving group, alkenyl or substituted phenyl; R2 and R5 independently = H, OH, SH, etc.; R3 and R4 independently = H, NH2, halo, etc. or the compound is a dimer with each monomer being of formula I, where the R3 and R4 groups of each monomer form together a dimer bridge -X-R-X-; R = alkylene group, which may be interrupted by heteroatoms or aromatic rings; X = O, S or NH; R6 = carbamate-based N-protecting group; R7 = oxygen protecting group or OH or R6 and R7 together form double bond between N10 and C11] and their pharmaceutically acceptable salts, are prepared and disclosed as antitumor agents. Thus, e.g., II was prepared by palladium catalyzed coupling of III (preparation given) with trans-propenylboronic acid followed by deprotection. The in vitro cytotoxicity of I towards K562 human chronic myeloid leukemia cells was evaluated using ELISA assay and it was revealed that selected compds. of the invention displayed IC50 values of less than 1  $\mu$ M. I should prove useful in the treatment of proliferative diseases such as leukemia. Pharmaceutical compns. comprising I are disclosed.

IT 864754-61-0P 864754-63-2P 864754-66-5P  
 864754-70-1P 864754-72-3P 864754-74-5P

864754-75-6P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

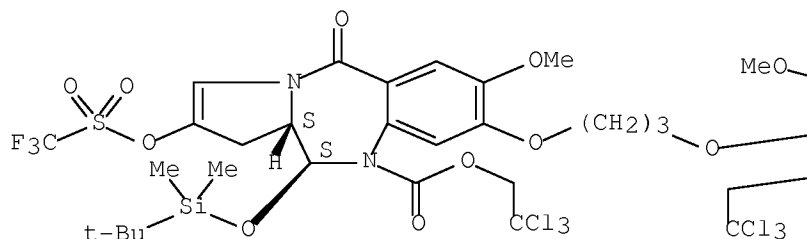
(preparation of pyrrolobenzodiazepinone derivs. as antitumor agents)

RN 864754-61-0 CAPLUS

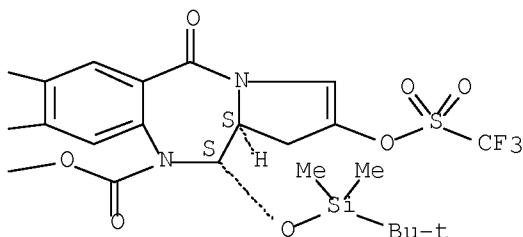
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-11,11a-dihydro-7-methoxy-5-oxo-2-[[[(trifluoromethyl)sulfonyl]oxy]-, bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



PAGE 1-B



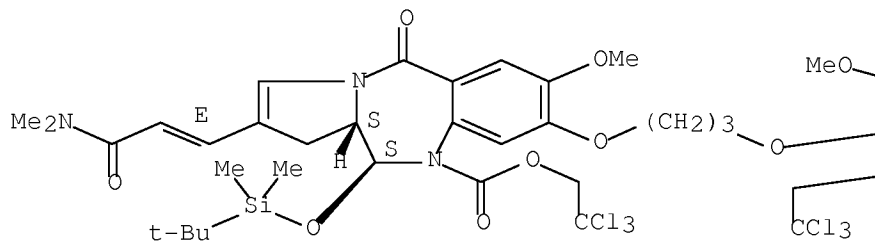
RN 864754-63-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2-[(1E)-3-(dimethylamino)-3-oxo-1-propenyl]-11-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-11,11a-dihydro-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

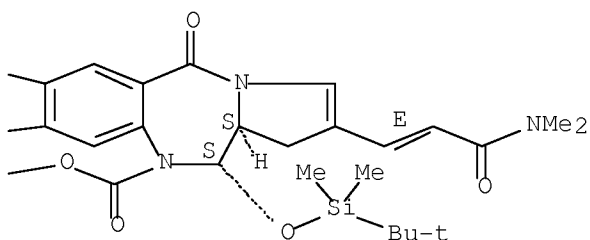
Absolute stereochemistry. Rotation (+).

Double bond geometry as shown.

PAGE 1-A



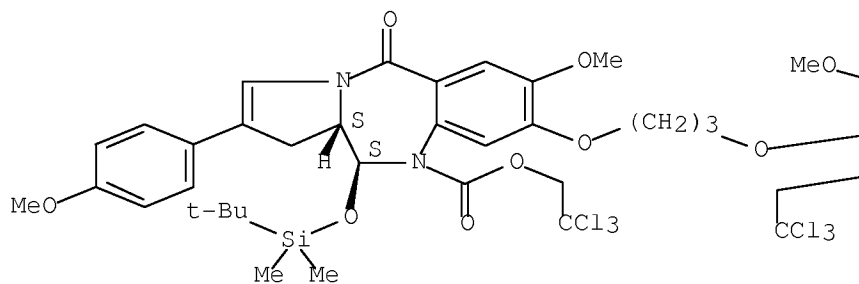
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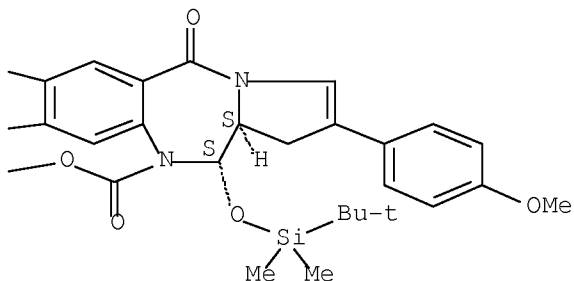


RN 864754-66-5 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[[(1,1-dimethylethyl)dimethylsilyl]ox  
 y]-11,11a-dihydro-7-methoxy-2-(4-methoxyphenyl)-5-oxo-,  
 bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
 NAME)

Absolute stereochemistry.

PAGE 1-A

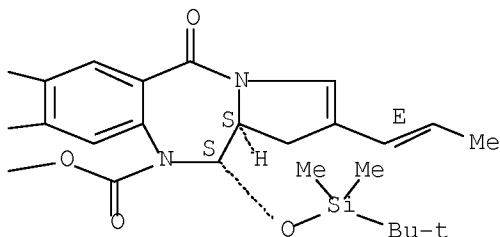
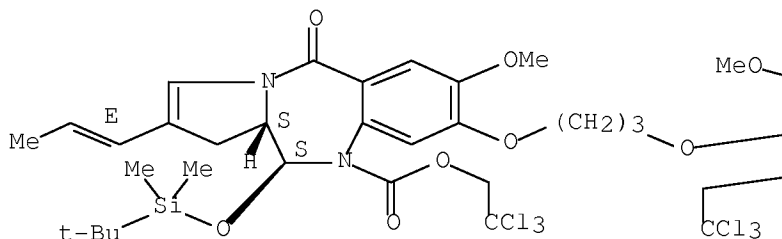




RN 864754-70-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]ox  
y]-11,11a-dihydro-7-methoxy-5-oxo-2-(1E)-1-propenyl-, bis(2,2,2-  
trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.

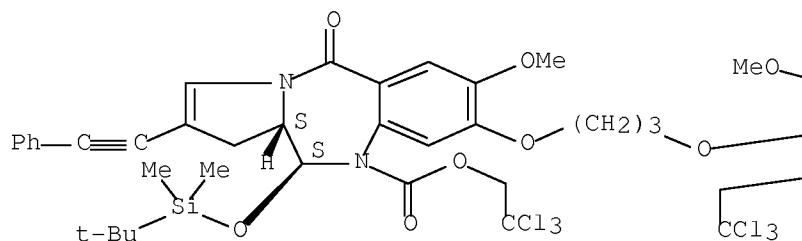


RN 864754-72-3 CAPLUS

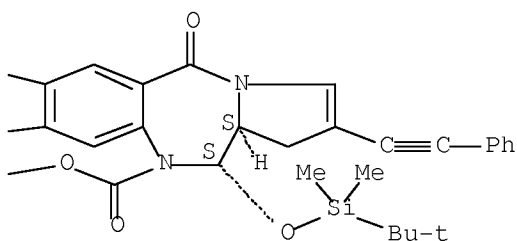
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]ox  
y]-11,11a-dihydro-7-methoxy-5-oxo-2-(phenylethynyl)-, bis(2,2,2-  
trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



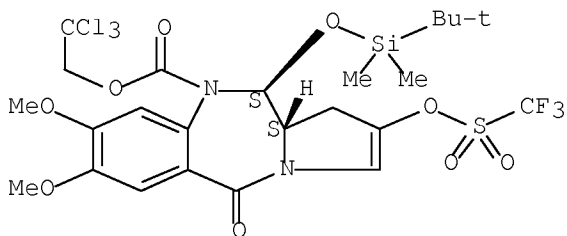
PAGE 1-B



RN 864754-74-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
11-[[ (1,1-dimethylethyl)dimethylsilyl]oxy]-11,11a-dihydro-7,8-dimethoxy-5-  
oxo-2-[[ (trifluoromethyl)sulfonyl]oxy]-, 2,2,2-trichloroethyl ester,  
(11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



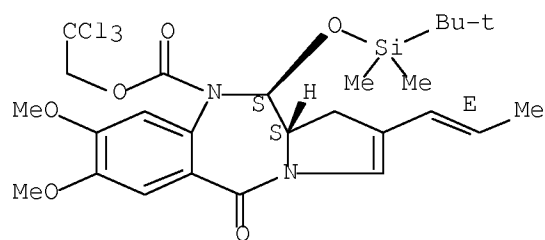
RN 864754-75-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
11-[[ (1,1-dimethylethyl)dimethylsilyl]oxy]-11,11a-dihydro-7,8-dimethoxy-5-  
oxo-2-(1E)-1-propen-1-yl-, 2,2,2-trichloroethyl ester, (11S,11aS)- (CA  
INDEX NAME)

Absolute stereochemistry. Rotation (+).

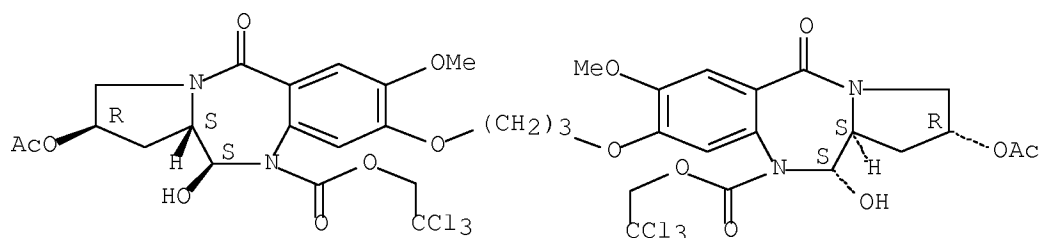


Double bond geometry as shown.



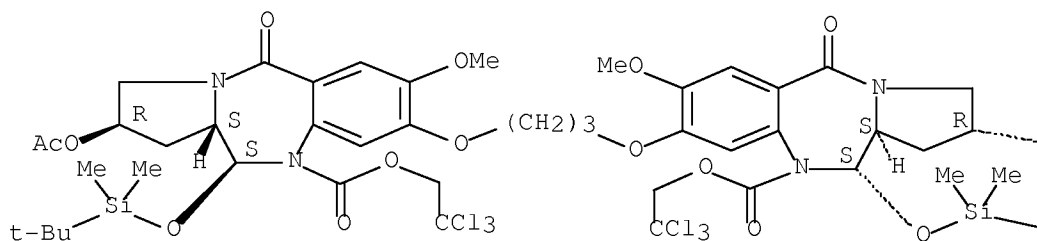
IT 864755-08-8P 864755-09-9P 864755-10-2P  
 864755-11-3P 864755-16-8P 864755-17-9P  
 864755-18-0P 864755-19-1P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (preparation of pyrrolobenzodiazepine derivs. as antitumor agents)  
 RN 864755-08-8 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[2-(acetyloxy)-2,3,11,11a-tetrahydro-11-  
 hydroxy-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester,  
 (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 864755-09-9 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[2-(acetyloxy)-11-[[1,1-  
 dimethylethyl]dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-,  
 bis(2,2,2-trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA  
 INDEX NAME)

Absolute stereochemistry.

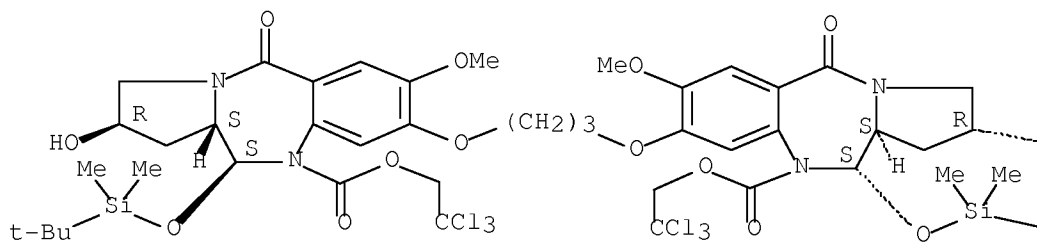


--- OAc

--- Bu-t

RN 864755-10-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[[(1,1-dimethylethyl)dimethylsilyl]ox  
 y]-2,3,11a-tetrahydro-2-hydroxy-7-methoxy-5-oxo-, bis(2,2,2-  
 trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
 NAME)

Absolute stereochemistry.



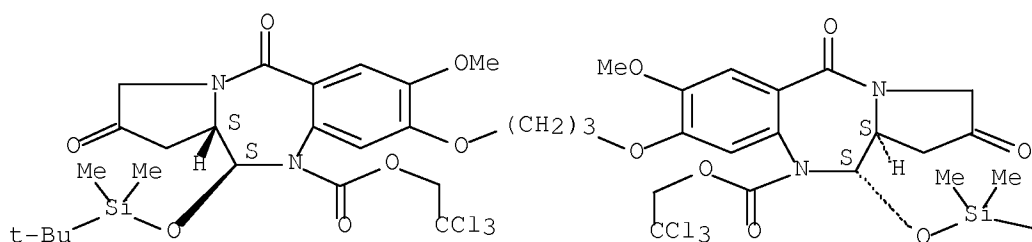
---OH

---Bu-t

RN 864755-11-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]oxy]  
-2,3,11,11a-tetrahydro-7-methoxy-2,5-dioxo-, bis(2,2,2-trichloroethyl)  
ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

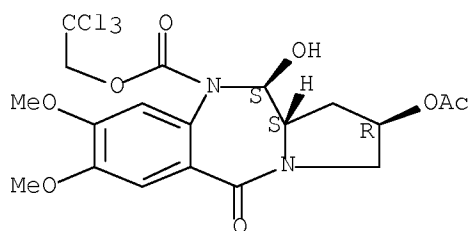


---Bu-t

RN 864755-16-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2-(acetyloxy)-2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-,  
2,2,2-trichloroethyl ester, (2R,11S,11aS)- (9CI) (CA INDEX NAME)

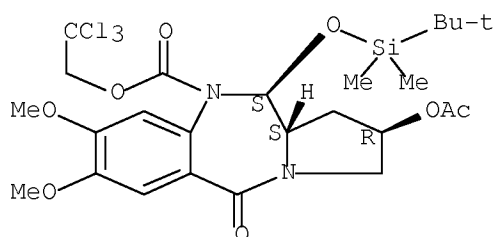
Absolute stereochemistry. Rotation (+).



RN 864755-17-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2-(acetyloxy)-11-[[1,1-dimethylethyl]dimethylsilyl]oxy]-2,3,11,11a-  
tetrahydro-7,8-dimethoxy-5-oxo-, 2,2,2-trichloroethyl ester,  
(2R,11S,11aS)- (9CI) (CA INDEX NAME)

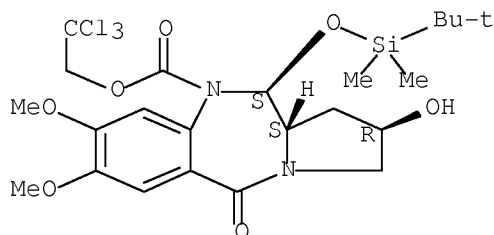
Absolute stereochemistry. Rotation (+).



RN 864755-18-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
11-[[1,1-dimethylethyl]dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-2-hydroxy-  
7,8-dimethoxy-5-oxo-, 2,2,2-trichloroethyl ester, (2R,11S,11aS)- (9CI)  
(CA INDEX NAME)

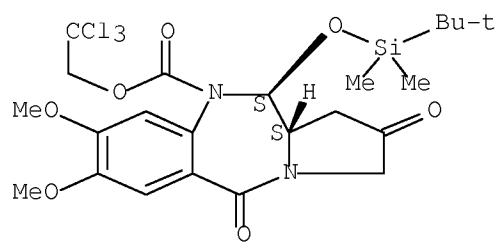
Absolute stereochemistry. Rotation (+).



RN 864755-19-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
11-[[1,1-dimethylethyl]dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-7,8-  
dimethoxy-2,5-dioxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (9CI) (CA  
INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 10 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:1004747 CAPLUS Full-text  
 DN 143:306347  
 TI Preparation of C8/C8' linked 5-oxo-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c]-  
 1,4-benzodiazepine dimers with 1H-pyrrole-dicarboxylic acid amide linkers  
 and oligomeric analogs thereof as well as related compounds for the  
 treatment of proliferative diseases  
 IN Howard, Philip Wilson; Gregson, Stephen John; Tiberghien, Arnaud Charles  
 PA Spirogen Limited, UK  
 SO PCT Int. Appl., 108 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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	NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM,				
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	RW:				
	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,				
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PRAI	GB 2004-4578	A	20040301		
	WO 2005-GB767	W	20050301		
OS	CASREACT 143:306347; MARPAT 143:306347				
GI					

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Title compds. I [Z = AYX(Het)naL(Het)nbL(Het)ncT(Het')ndL(Het')neL(Het')nf  
 X'Y'A'; A = O, S, NH, or bond; Y = divalent group or single bond; X and X' are  
 both either NH or CO; Het and Het' independently = aminoheteroarylenecarbonyl;  
 each L independently =  $\beta$ -alanine, glycine, 4-aminobutanoic acid or single  
 bond; T = divalent linker group; A', Y' are independently selected definitions  
 for A and Y; na, mb, mc, nd, ne, nf independently = 0-5 with their sum = 0-16;  
 R2 and R3 = H, OH, CN, etc.; R6, R7 and R9 independently = H, SH, NH<sub>2</sub>, NO<sub>2</sub>,  
 etc.; R10 = N-protecting group; R15 = OH, =O, =S, OR where R = protecting  
 group; R10 and R15 may together form a double bond between atoms to which they  
 are attached], and their pharmaceutically acceptable salts, are prepared and  
 disclosed as antiproliferative agents. Thus, e.g., II was prepared by  
 bischlorination of N-methyl-2,5-pyrroledicarboxylic acid followed by  
 bisamidation with aniline III and removal of N-protecting group. I were  
 evaluated for DNA crosslinking ability, in vitro cytotoxicity in human chronic  
 myeloid leukemia cells and screened against 60 human tumor cell lines. For  
 example, compound II demon stated an IC<sub>50</sub> of 1.2  $\mu$ M in in vitro cytotoxicity  
 assay and a GI<sub>50</sub> of 1.0  $\mu$ M in tumor cell screening. Further aspects of the

present invention relate to their use in the manufacture of a medicament for the treatment of a proliferative disease.

IT 864672-61-7P 864672-62-8P 864672-66-2P  
864672-67-3P 864672-68-4P 864672-70-8P  
864672-71-9P 864672-72-0P 864672-73-1P  
864672-75-3P 864672-77-5P 864672-78-6P  
864672-79-7P 864672-81-1P 864672-83-3P  
864672-90-2P 864672-92-4P 864672-95-7P  
864672-96-8P

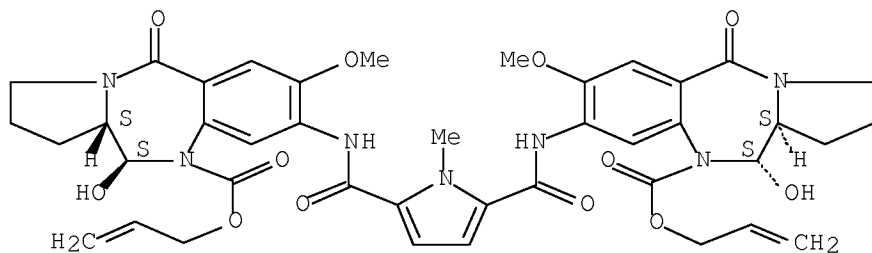
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of oxotetrahydropyrrolobenzodiazepine dimers containing pyrroledicarboxylic acid amide linkers and oligomeric analogs thereof as antiproliferative agents)

RN 864672-61-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[(1-methyl-1H-pyrrole-2,5-diyl)bis(carbonylimino)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

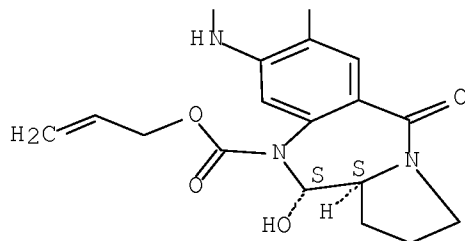
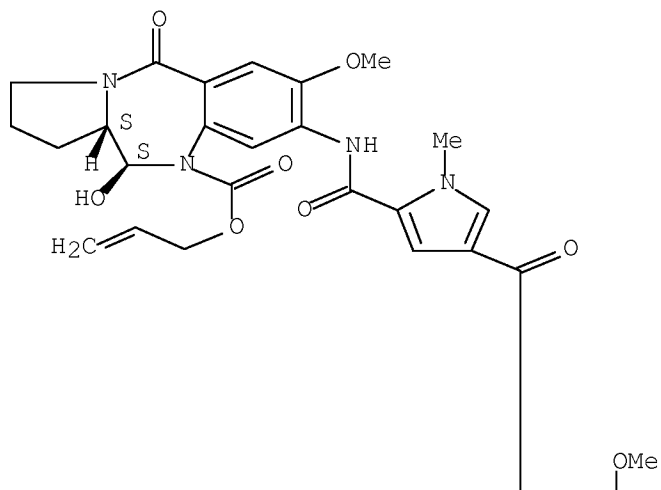
Absolute stereochemistry. Rotation (+).



RN 864672-62-8 CAPLUS

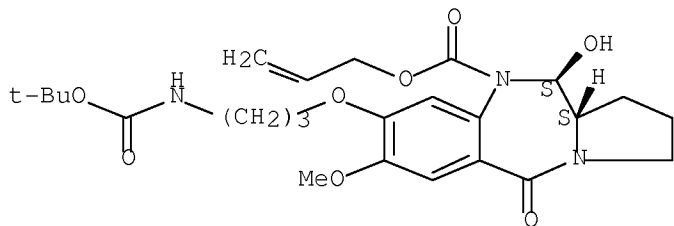
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[[[4-[[[(11S,11aS)-2,3,5,10,11,11a-hexahydro-11-hydroxy-7-methoxy-5-oxo-10-[(2-propen-1-yloxy)carbonyl]-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 864672-66-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-[3-[[ (1,1-dimethylethoxy)carbonyl]amino]propoxy]-2,3,11,11a-tetrahydro-  
 11-hydroxy-7-methoxy-5-oxo-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX  
 NAME)

Absolute stereochemistry.

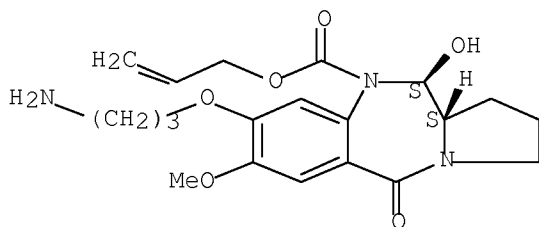


RN 864672-67-3 CAPLUS



CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(3-aminopropoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

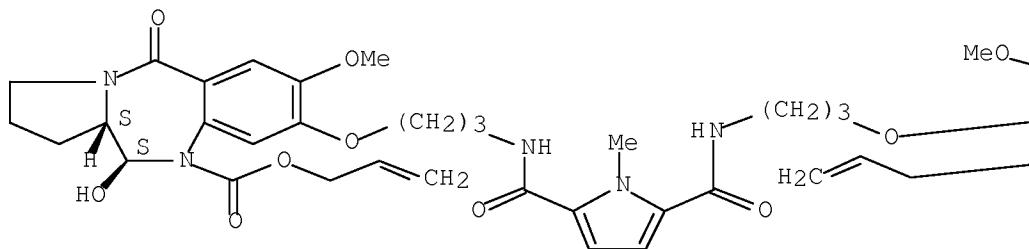


RN 864672-68-4 CAPLUS

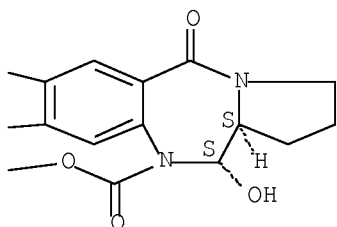
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[(1-methyl-1H-pyrrole-2,5-diyl)bis(carbonylimino-3,1-  
propanediylloxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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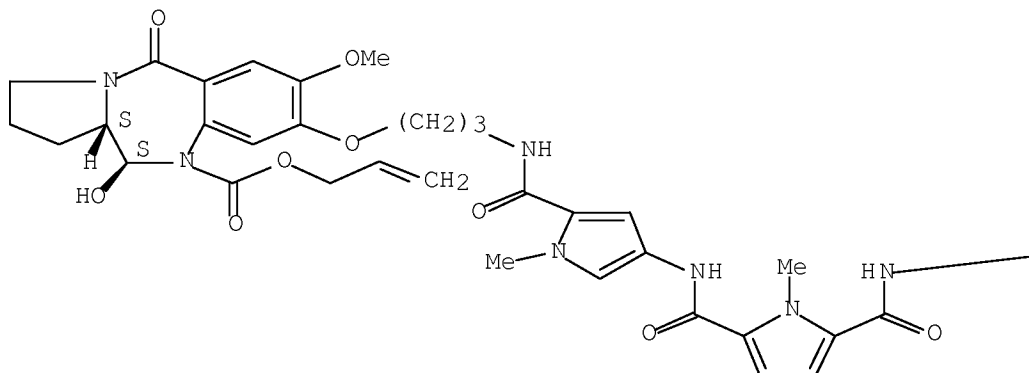
RN 864672-70-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[(1-methyl-1H-pyrrole-2,5-diyl)bis[carbonylimino(1-methyl-1H-pyrrole-

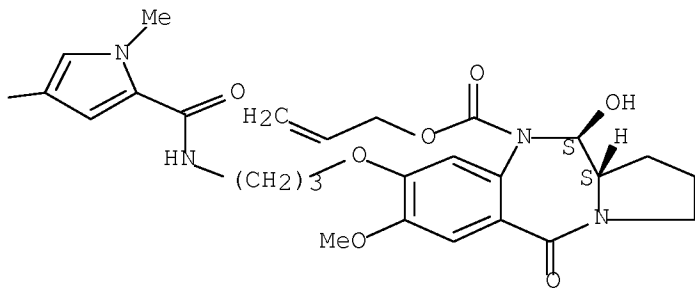
4,2-diyl)carbonylimino-3,1-propanediyl]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

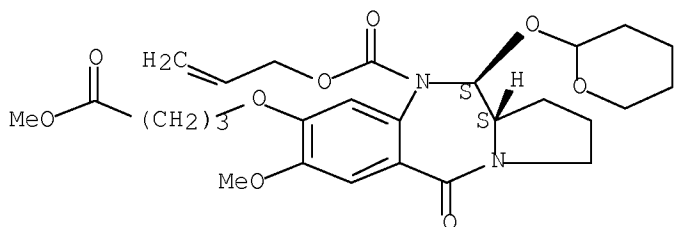


PAGE 1-B



RN 864672-71-9 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-7-methoxy-8-(4-methoxy-4-oxobutoxy)-5-oxo-11-  
 [(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA  
 INDEX NAME)

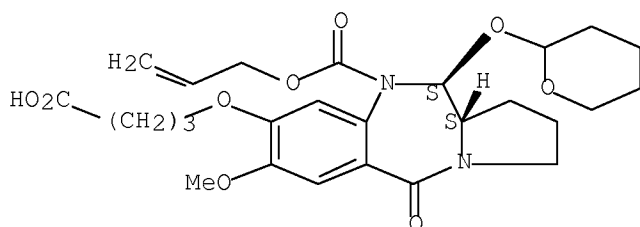
Absolute stereochemistry.



RN 864672-72-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(3-carboxypropoxy)-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-  
2H-pyran-2-yl)oxy]-, 10-(2-propen-1-yl) ester, (11S,11aS)- (CA INDEX  
NAME)

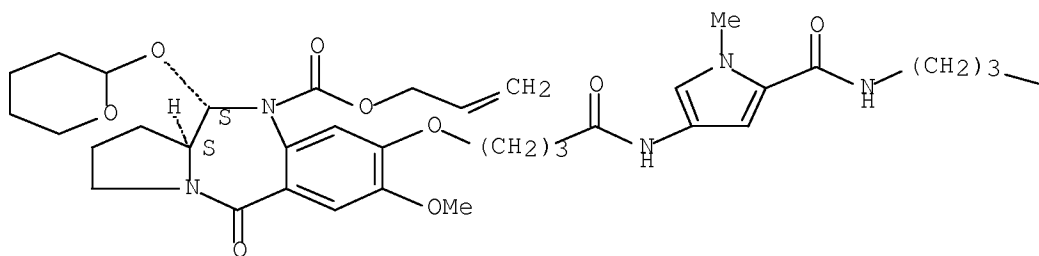
Absolute stereochemistry.



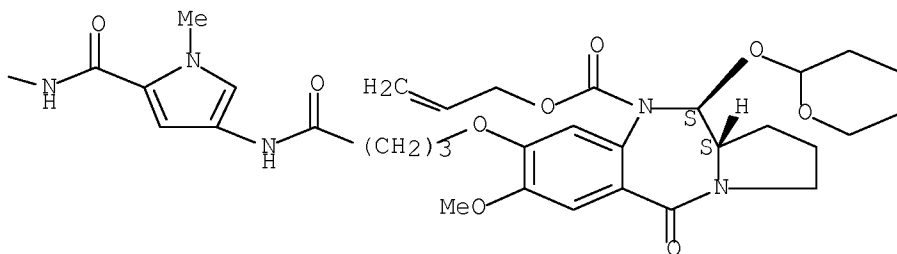
RN 864672-73-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-pyrrole-2,4-  
diyl)imino(4-oxo-4,1-butanediyl)oxy]]bis[2,3,11,11a-tetrahydro-7-methoxy-5-  
oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, di-2-propenyl ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



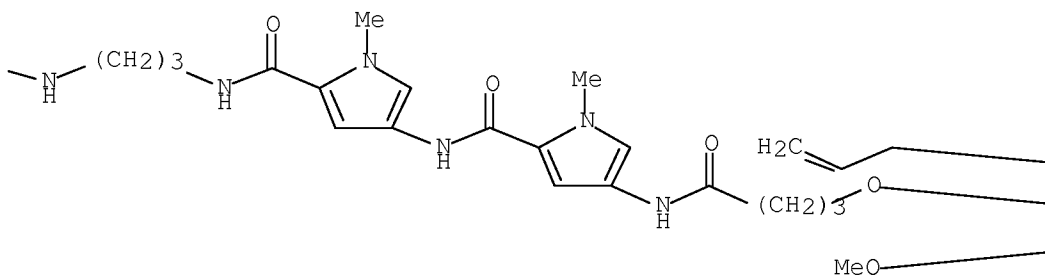
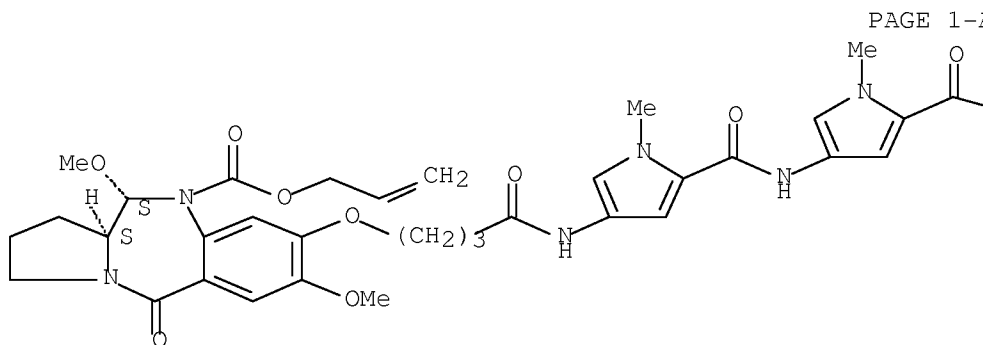
PAGE 1-A

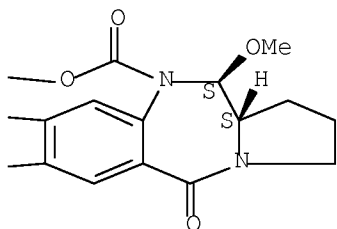


RN 864672-75-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-pyrrole-2,4-  
diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)imino(4-oxo-4,1-  
butanediyl)oxy]]bis[2,3,11,11a-tetrahydro-7,11-dimethoxy-5-oxo-,  
di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

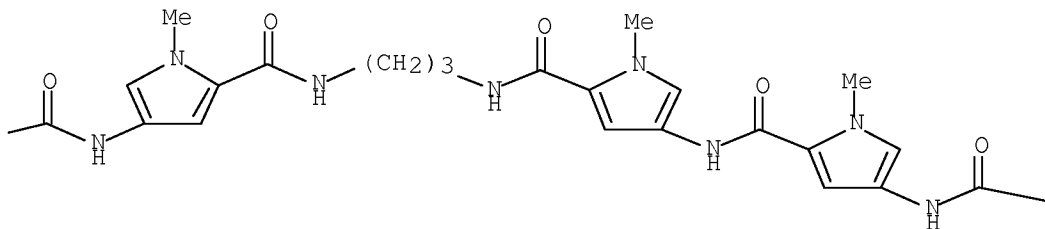
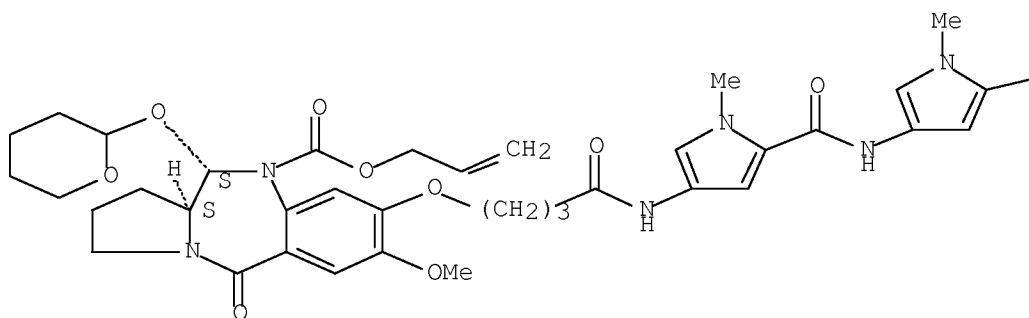


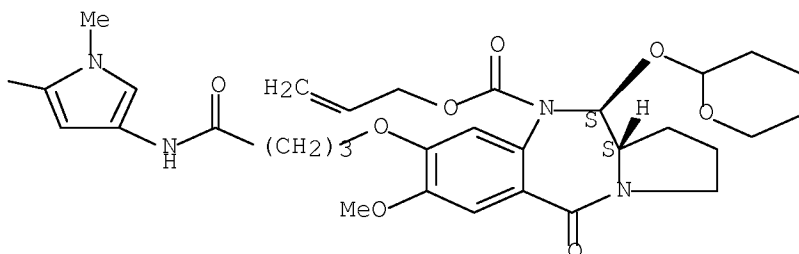


RN 864672-77-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-pyrrole-2,4-  
diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)iminocarbonyl(1-methyl-1H-  
pyrrole-2,4-diyl)imino(4-oxo-4,1-butanediyl)oxy]]bis[2,3,11,11a-tetrahydro-  
7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, di-2-propenyl ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

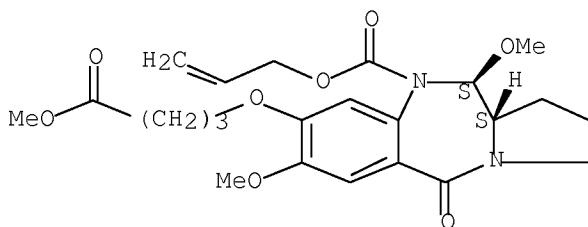




RN 864672-78-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7,11-dimethoxy-8-(4-methoxy-4-oxobutoxy)-5-oxo-,  
2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

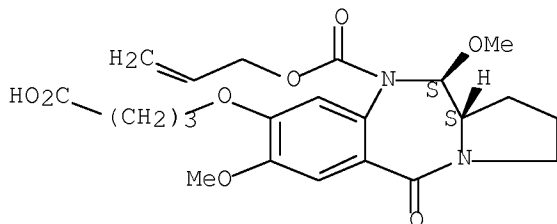
Absolute stereochemistry.



RN 864672-79-7 CAPLUS

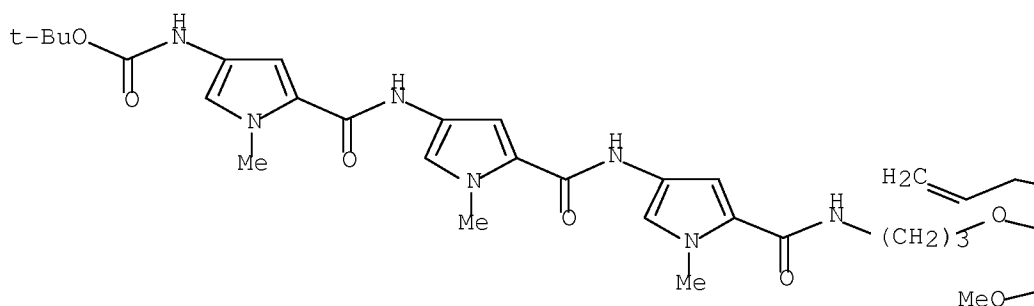
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(3-carboxypropoxy)-2,3,11,11a-tetrahydro-7,11-dimethoxy-5-oxo-,  
10-(2-propen-1-yl) ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

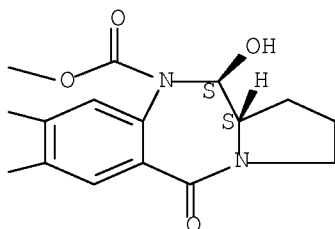


CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[3-[[[4-[[[4-[[[4-[(1,1-dimethylethoxy)carbonyl]amino]-1-methyl-1H-  
pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-  
methyl-1H-pyrrol-2-yl]carbonyl]amino]propoxy]-2,3,11,11a-tetrahydro-11-  
hydroxy-7-methoxy-5-oxo-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX  
NAME)

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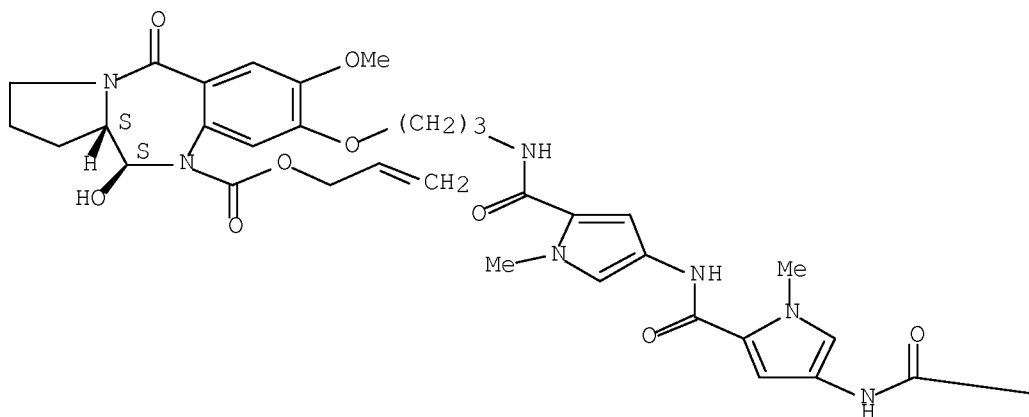
PAGE 1-B



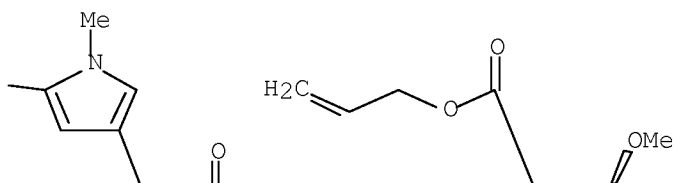
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[3-[[[4-[[[4-[[[4-[[[4-[(11S,11aS)-2,3,5,10,11,11a-hexahydro-7,11-  
dimethoxy-5-oxo-10-[(2-propen-1-yloxy)carbonyl]-1H-pyrrolo[2,1-  
c][1,4]benzodiazepin-8-yl]oxy]-1-oxobutyl]amino]-1-methyl-1H-pyrrol-2-  
yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-  
pyrrol-2-yl]carbonyl]amino]propoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-  
methoxy-5-oxo-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

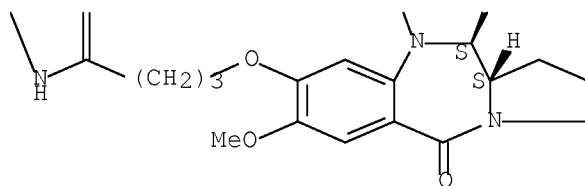
PAGE 1-A



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PAGE 2-B



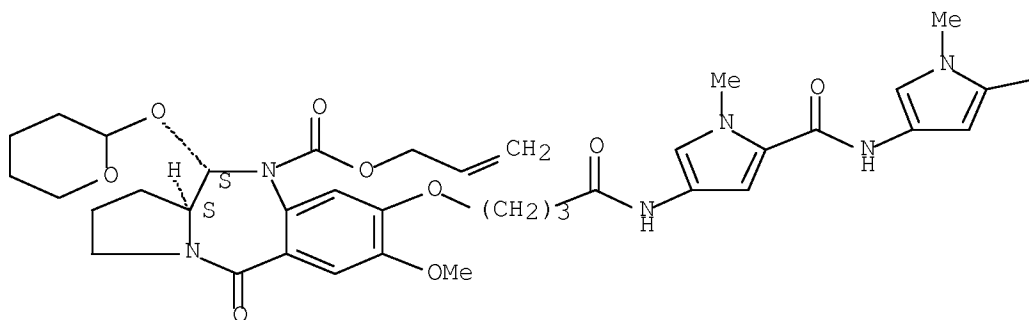
RN 864672-90-2 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,



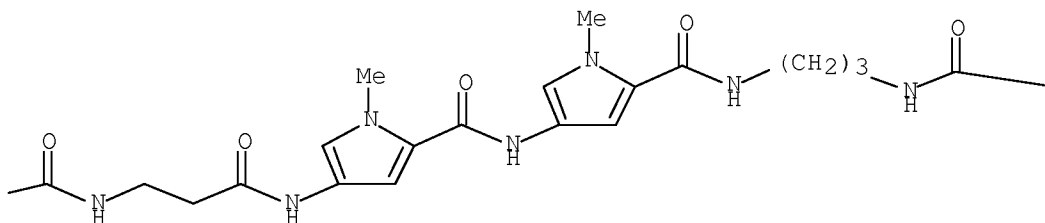
8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)imino(3-oxo-3,1-propanediyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)imino(4-oxo-4,1-butanediyl)oxy]]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

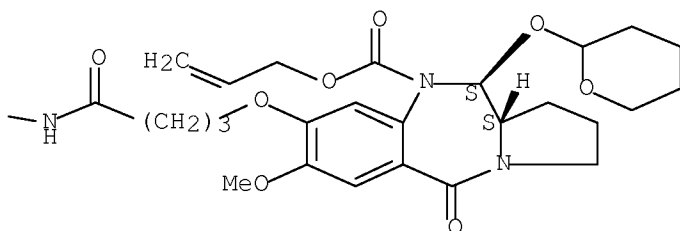
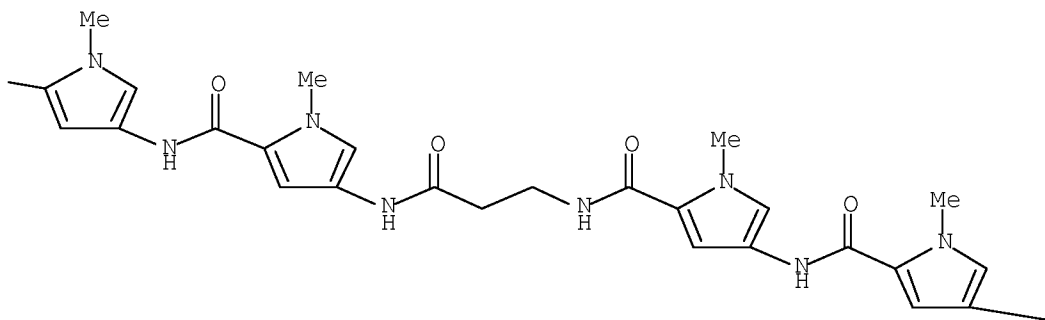
Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

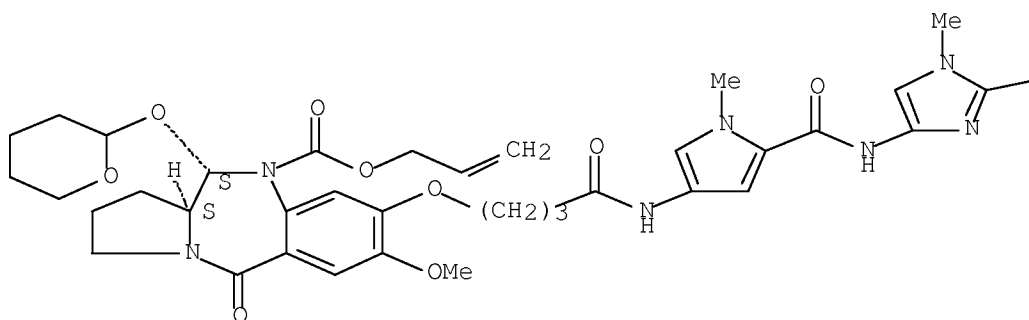




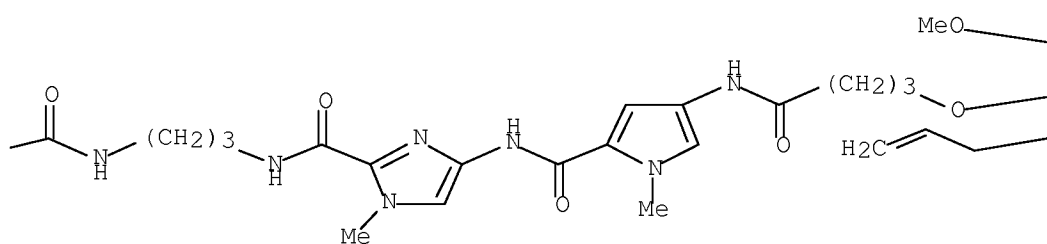
RN	864672-92-4	CAPLUS
CN	1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-imidazole-2,4- diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)imino(4-oxo-4,1- butanediyl)oxy]]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro- 2H-pyran-2-yl)oxy]-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)	

Absolute stereochemistry.

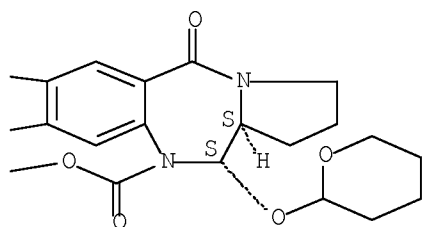
PAGE 1-A



PAGE 1-B



PAGE 1-C

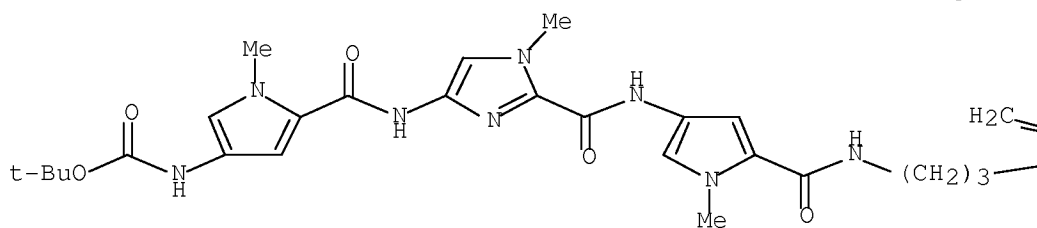


RN 864672-95-7 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-[3-[[[4-[[[4-[[[4-[[[(1,1-dimethylethoxy)carbonyl]amino]-1-methyl-1H-  
 pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-  
 methyl-1H-pyrrol-2-yl]carbonyl]amino]propoxy]-2,3,11,11a-tetrahydro-11-  
 hydroxy-7-methoxy-5-oxo-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX

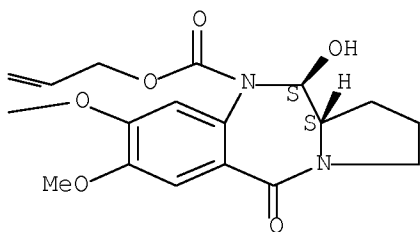
NAME)

Absolute stereochemistry. Rotation (+).

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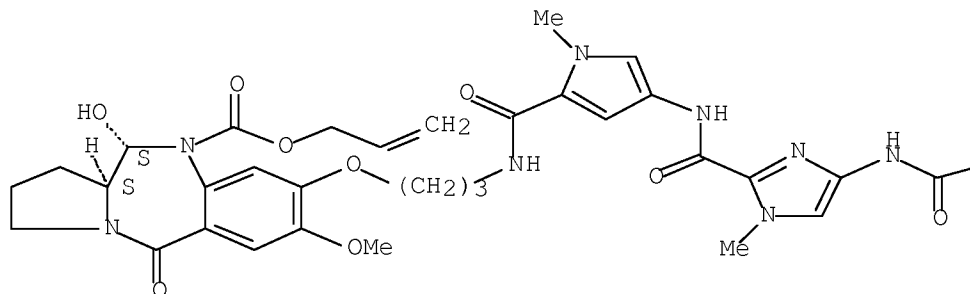
PAGE 1-B

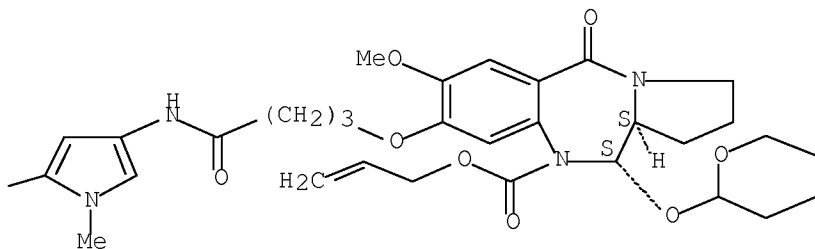


RN 864672-96-8 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[4-[[5-[[[2-[[[5-[[[3-[[[11S,11aS)-2,3,5,10,11,11a-hexahydro-11-hydroxy-  
7-methoxy-5-oxo-10-[(2-propen-1-yloxy)carbonyl]-1H-pyrrolo[2,1-  
c][1,4]benzodiazepin-8-yl]oxy]propyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-  
yl]amino]carbonyl]-1-methyl-1H-imidazol-4-yl]amino]carbonyl]-1-methyl-1H-  
pyrrol-3-yl]amino]-4-oxobutoxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA  
INDEX NAME)

Absolute stereochemistry.

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IT 600713-85-7 864672-97-9

RL: RCT (Reactant); RACT (Reactant or reagent)

(starting material; preparation of oxotetrahydropyrrolobenzodiazepine

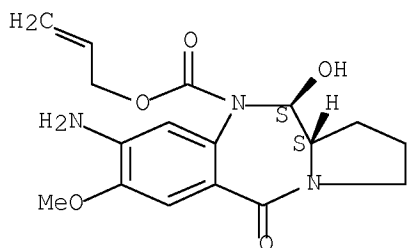
dimers

containing pyrroledicarboxylic acid amide linkers and oligomeric analogs thereof as antiproliferative agents)

RN 600713-85-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-amino-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

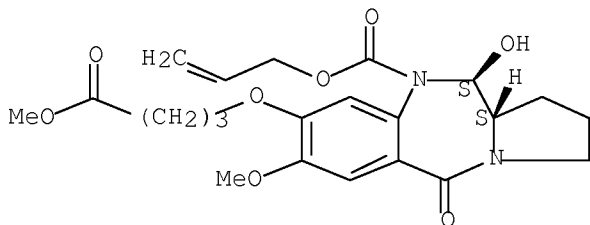
Absolute stereochemistry.



RN 864672-97-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(4-methoxy-4-oxobutoxy)-5-oxo-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 11 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:1004692 CAPLUS Full-text

DN 143:286420

TI Preparation of aminobiaryl carboxylic acids for the manufacture of medicaments for treating proliferative disease

IN Howard, Philip Wilson; Wells, Geoffrey

PA Spirogen Limited, UK

SO PCT Int. Appl., 90 pp.

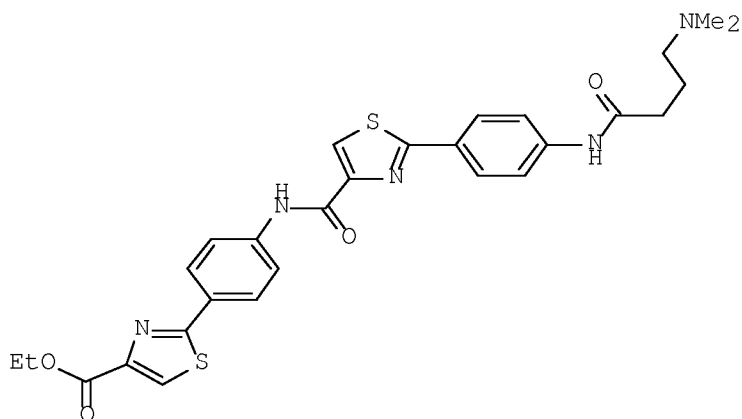
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 2005085177	A2	20050915	WO 2005-GB752	20050301
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	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1727808	A2	20061206	EP 2005-717831	20050301
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
	US 20070249591	A1	20071025	US 2007-591140	20070108
PRAI	GB 2004-4574	A	20040301		
	WO 2005-GB752	W	20050301		
OS	CASREACT 143:286420; MARPAT 143:286420				
GI					



I

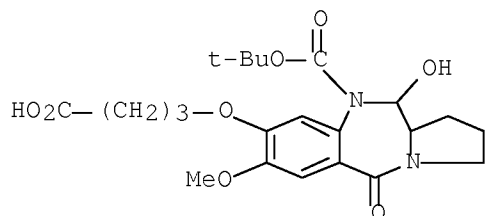
AB The invention relates to aminobiaryl carboxylic acids Z'-CO-A-B-NH-Z (Z is H or a protecting group, Z' is OH, Cl or a protected or activated hydroxyl group, A, B are optionally substituted C5-6 arylene groups), including their synthesis and use in synthesizing mols. designed to interact with DNA. Thus, aminophenylthiazolecarboxylic acid derivative I was prepared by amidation reactions and assessed for binding to DNA. Compound I produces an unusual

IT 864076-50-6

(preparation of aminobiaryl carboxylic acids for manufacture of medicaments for treating proliferative disease)

RN 864076-50-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(3-carboxypropoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
10-(1,1-dimethylethyl) ester (CA INDEX NAME)

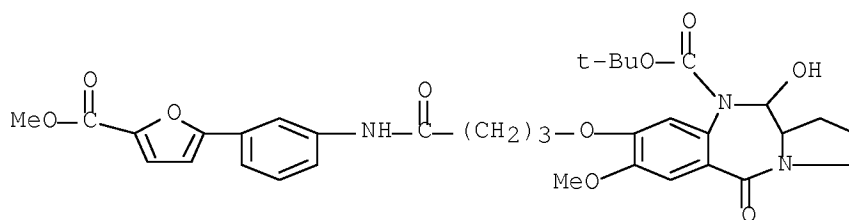


IT 864076-47-1P

(preparation of aminobiaryl carboxylic acids for manufacture of medicaments for treating proliferative disease)

RN 864076-47-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-[4-[3-[5-(methoxycarbonyl)-2-  
furanyl]phenyl]amino]-4-oxobutoxy]-5-oxo-, 1,1-dimethylethyl ester (CA  
INDEX NAME)



L11 ANSWER 12 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:395315 CAPLUS Full-text  
 DN 142:447059  
 TI Method for preparation of pyrrolobenzodiazepine derivatives and  
 compositions comprising them  
 IN Vishnuvajjala, B. Rao; Liu, Paul S.; Snader, Kenneth M.; Thurston, David;  
 Howard, Philip W.; Turner, Gregory  
 PA Government of the United States of America, Represented by the Secretary  
 Department of Health and Human Services, USA; Spirogen, Ltd.; Starks  
 Associates, Inc.; Midwest Research Institute; Hsiao, Luke Y.  
 SO PCT Int. Appl., 89 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005040170	A2	20050506	WO 2004-US35050	20041022
	WO 2005040170	A3	20050630		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
	RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	AU 2004284075	A1	20050506	AU 2004-284075	20041022
	CA 2543318	A1	20050506	CA 2004-2543318	20041022
	EP 1675857	A2	20060705	EP 2004-817338	20041022
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR			
	US 20070072846	A1	20070329	US 2006-576689	20060814
PRAI	US 2003-513751P	P	20031022		
	WO 2004-US35050	W	20041022		
OS	CASREACT 142:447059; MARPAT 142:447059				
GI					

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Disclosed is: compds. I [X = OH, ether, silyl ether, trialkylsilyl ether, ester, carbonate, (cyclic) carbamate, (cyclic) thiocarbamate, OAc, SH, sulfide, sulfoxide, sulfone, sulfite, bisulfite, sulfonamide, amine, amide, N3, CN, halogen, triphenylphosphonium, silyl, trialkylsilyl, amino acid, phosphorus-containing group; Y = H, X; R1, R2 = H, C1-8-alkyl, aryl, heterocycle; R3, R4, R8 = H, (un)substituted C1-24-alkyl, C2-24-alkenyl, C2-24-alkynyl, (un)substituted aryl; R5, R6 = H, C1-8-alkyl, aryl, heterocycle; R7 = H, absent; T1, T2 = O, S, NR8; Z = divalent radical of (un)substituted alkane, alkene, alkyne (optionally containing a heteroatom or a carbonyl); p =  $\geq 2$ ; with the proviso that when dashed line from CY to NR7 is a double bond, R7 is absent & Y = H and with dashed line is a single bond R7 = H & Y = X; with the proviso that when the dashed line to R1 is a double bond, then R2 is absent; with the proviso that when the dashed line to R5 is a double bond, then R6 is absent] or a salt thereof, wherein the compound is a solid. Also



disclosed are: a pharmaceutical composition comprising a compound I and a carrier; a method of inhibiting growth of a cell, which method comprises administering in an amount effective to inhibit growth a compound I; a method of treating cancer in a mammal, which method comprises administering in an amount effective to treat cancer a compound I; a method of treating a viral, parasitic, or bacterial infection of a cell, which method comprises administering in an amount effective to treat a viral, parasitic, or bacterial infection a compound I; and a method of preparing a compound I as described herein. The method of preparation of I comprises: (a) providing a compound II; and (b) reaction II with a nucleophile, e.g. water, an alc., a thiol or an amine, to give the crystalline solid I. Thus, dimer III [A = (CH<sub>2</sub>)<sub>3</sub>] was prepared from 4-HO-3-MeOC<sub>6</sub>H<sub>3</sub>CO<sub>2</sub>Me and trans-4-hydroxy-L-proline via coupling of diacid IV [A = (CH<sub>2</sub>)<sub>3</sub>] with trans-4-hydroxy-L-prolinol derivative V [TBDMS = SiMe<sub>2</sub>CMe<sub>3</sub>] and oxidative cyclization of bisamide VI [A = (CH<sub>2</sub>)<sub>3</sub>]. The in vitro antitumor activity of III [A = (CH<sub>2</sub>)<sub>3</sub>] was determined [LC<sub>50</sub> = 28.2 nM vs. leukemia cell line HL-60(TB); LC<sub>50</sub> = 67.6 nM vs. non-small cell lung cell line NCI-H23; LC<sub>50</sub> = 251.2 nM vs. colon cell line COLO 205; LC<sub>50</sub> = 467.7 nM vs. CNS cell line SNB-75; LC<sub>50</sub> = 7.1 nM vs. melanoma cell line UACC-62; LC<sub>50</sub> = 1000 nM vs. ovarian cell line SK-OV-3; LC<sub>50</sub> = 1000 nM vs. renal cell line CAKI-1; LC<sub>50</sub> = 1000 nM vs. prostate cell line DU-145; LC<sub>50</sub> = 57.5 nM vs. breast cell line MDA-N].

IT 232931-64-5P

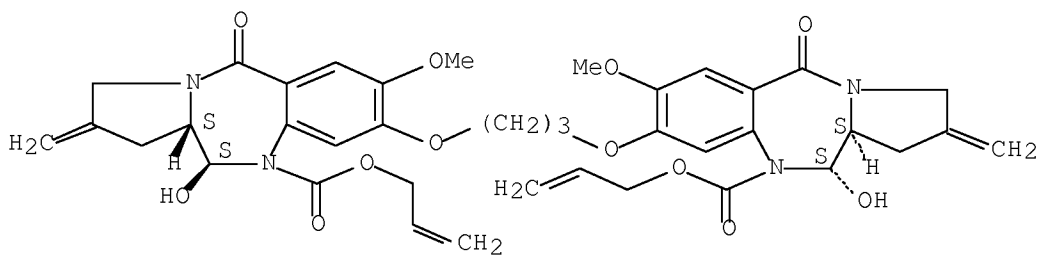
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and N-decarbonylation of; preparation of pyrrolobenzodiazepine derivs. as antitumor antibiotics and other medicinals)

RN 232931-64-5 CAPLUS

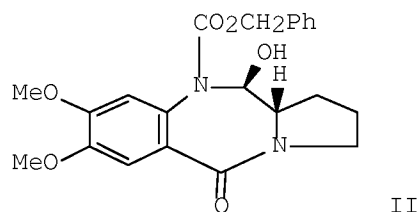
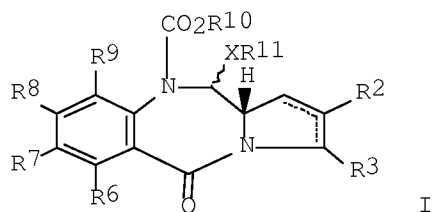
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 13 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:238991 CAPLUS Full-text  
 DN 142:316867  
 TI Synthesis of protected pyrrolobenzodiazepines  
 IN Howard, Philip; Masterson, Luke  
 PA Spirogen Limited, UK  
 SO PCT Int. Appl., 120 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005023814	A1	20050317	WO 2004-GB3873	20040910
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1664049	A1	20060607	EP 2004-768420	20040910
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
	IN 2006DN01149	A	20070810	IN 2006-DN1149	20060303
	US 20060264622	A1	20061123	US 2006-571274	20060309
PRAI	GB 2003-21295	A	20030911		
	WO 2004-GB3873	W	20040910		
OS	CASREACT 142:316867; MARPAT 142:316867				
GI					



AB Pyrrolobenzodiazepines I [R2, R3 = H, O, OH, CH2, CN, R, OR, O3SR, COR; R = (un)substituted alkyl, heterocyclcyl, aryl; R6, R7, R9 = H, R, OH, OR, SH, SR, NH2, NHR, NRR1, NO2, SnMe3, halogen; R1 = (un)substituted alkyl, heterocyclcyl, aryl; R8 = H, R, OH, OR, SH, SR, NH2, NHR, NRR1, NO2, SnMe3, halogen, XR4X; R4 = alkylene, heteroalkylene; X = O, S, NH; CO2R10 = protective group; R11 = H, R] were prepared by treating an isocyanatobenzoate with an alc. to form the carbamate, followed by (S)-2-pyrrolidinemethanol, cyclizing, optionally alkylating the resulting OH group. Thus, 2,4,5-O2N(MeO)2C6H2CO2H was amidated with (S)-2-pyrrolidinemethanol, followed by tert-butyldimethylsilyl protection, reduction of the nitro group, and conversion of the amine to isocyanate. The isocyanate was treated with benzyl alc. to give the benzyloxycarboylamine which was desilylated and cyclized with base to give the pyrrolobenzodiazepine II.

IT 461462-59-9P 848004-38-6P 848004-39-7P  
 848004-40-0P 848004-41-1P 848004-46-6P  
 848004-54-6P 848004-56-8P 848004-77-3P  
 848004-82-0P 848004-83-1P 848004-84-2P  
 848005-05-0P

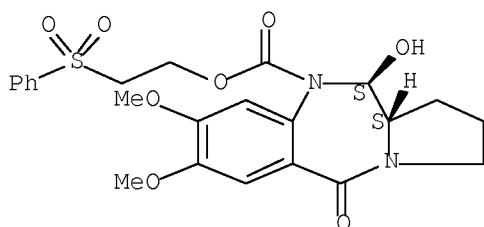
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of protected pyrrolobenzodiazepines)

RN 461462-59-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-, 2-(phenylsulfonyl)ethyl ester, (11S,11aS)- (CA INDEX NAME)

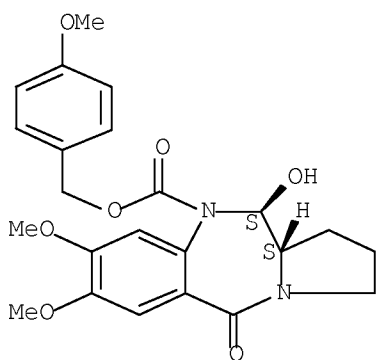
Absolute stereochemistry. Rotation (+).



RN 848004-38-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-, (4-methoxyphenyl)methyl ester, (11S,11aS)- (CA INDEX NAME)

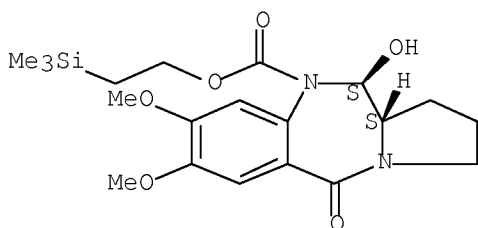
Absolute stereochemistry. Rotation (+).



RN 848004-39-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-,  
2-(trimethylsilyl)ethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

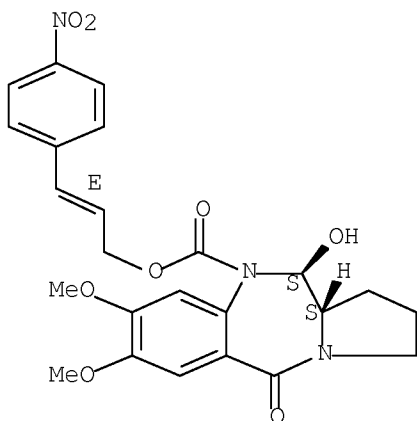


RN 848004-40-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-,  
(2E)-3-(4-nitrophenyl)-2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

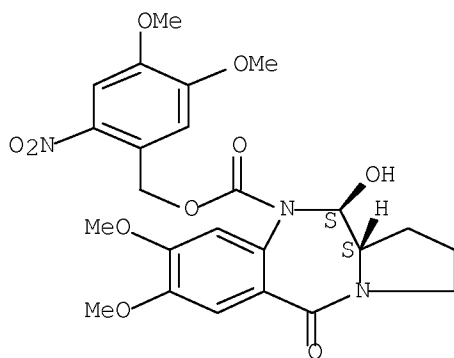
Absolute stereochemistry. Rotation (+).

Double bond geometry as shown.



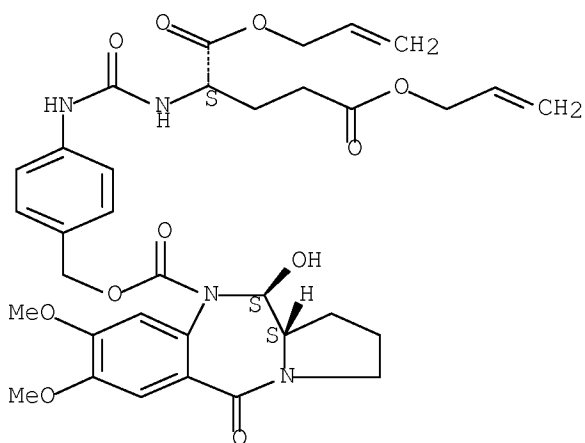
RN 848004-41-1 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-,  
 (4,5-dimethoxy-2-nitrophenyl)methyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



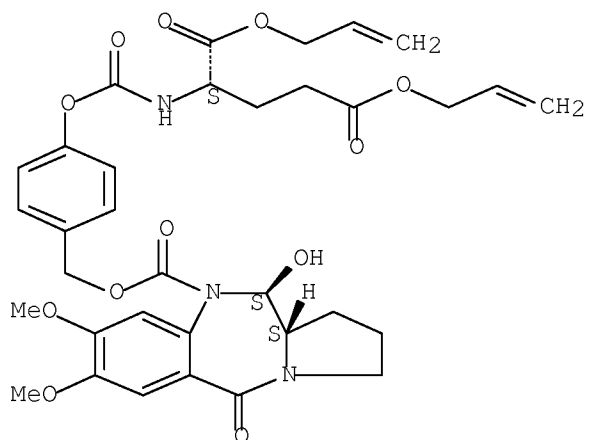
RN 848004-46-6 CAPLUS  
 CN L-Glutamic acid, N-[[[4-[[[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-yl]carbonyl]oxy]methyl]phenyl]amino]carbonyl]-, di-2-propenyl ester (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 848004-54-6 CAPLUS  
 CN L-Glutamic acid, N-[[[4-[[[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-yl]carbonyl]oxy]methyl]phenoxy]carbonyl]-, di-2-propenyl ester (9CI) (CA INDEX NAME)

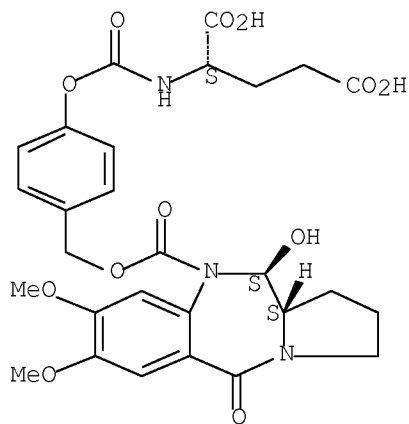
Absolute stereochemistry.



RN 848004-56-8 CAPLUS

CN L-Glutamic acid, N-[[4-[[[[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-yl]carbonyl]oxy]methyl]phenoxy]carbonyl]- (CA INDEX NAME)

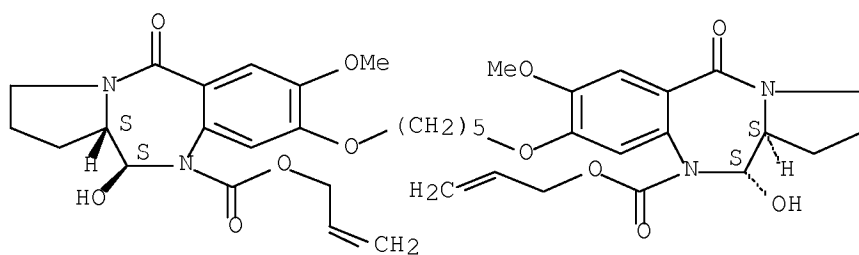
Absolute stereochemistry.



RN 848004-77-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentandiylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

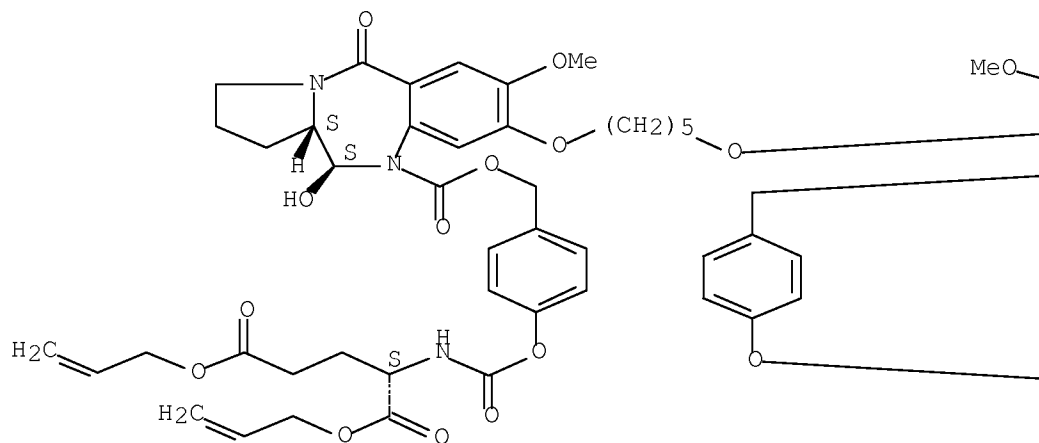


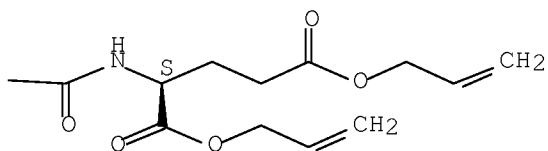
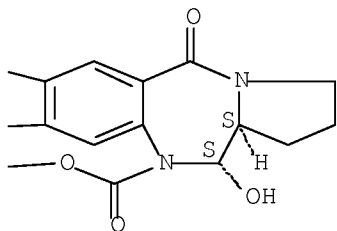
RN 848004-82-0 CAPLUS

CN L-Glutamic acid, N,N'-[1,5-pentanediyldis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneoxycarbonyl]]bis-, tetra-2-propenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A

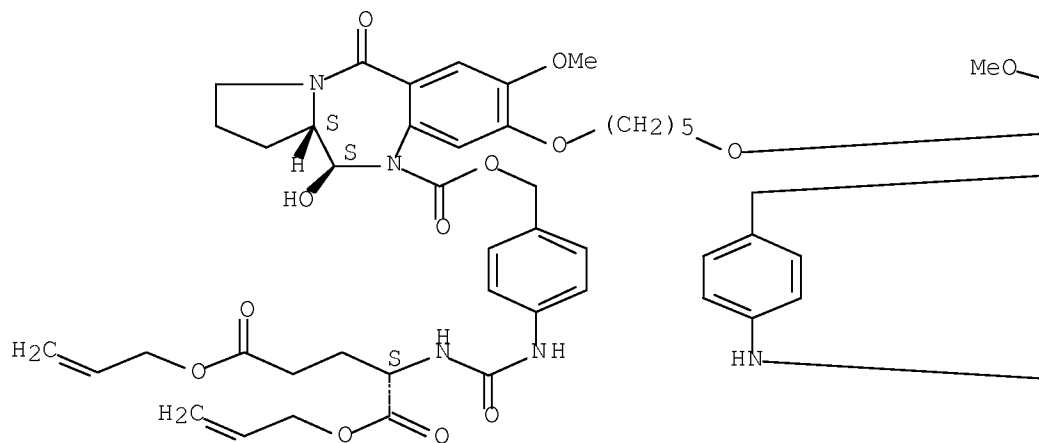




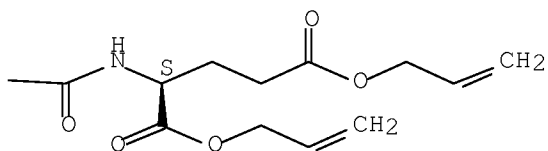
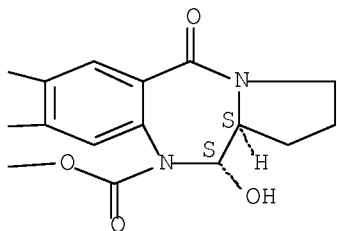
RN 848004-83-1 CAPLUS

CN L-Glutamic acid, N,N'-[1,5-pentanediy]bis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneiminocarbonyl]]bis-, tetra-2-propenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



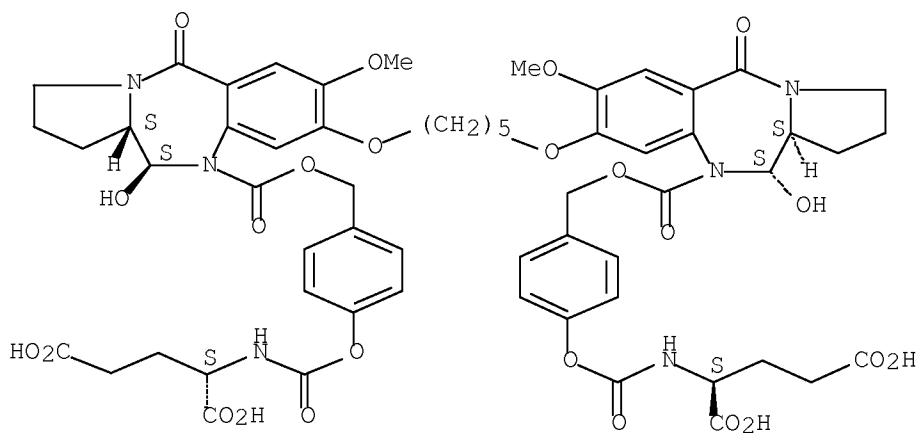




RN 848004-84-2 CAPLUS

CN L-Glutamic acid, N,N'-[1,5-pentanediyldis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneoxycarbonyl]]bis- (9CI)  
(CA INDEX NAME)

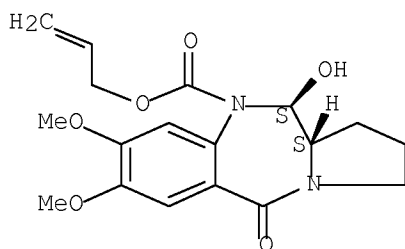
Absolute stereochemistry. Rotation (+).



RN 848005-05-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



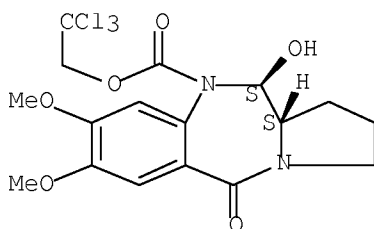
IT 260418-53-9P 848004-37-5P 848004-42-2P  
 848004-47-7P 848004-85-3P 848005-01-6P  
 848005-02-7P 848005-03-8P 848005-04-9P  
 848005-10-7P 848005-11-8P

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of protected pyrrolobenzodiazepines)

RN 260418-53-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-,  
 2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

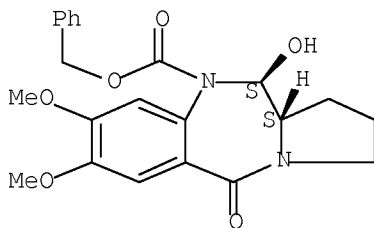
Absolute stereochemistry. Rotation (+).



RN 848004-37-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-, phenylmethyl ester,  
 (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

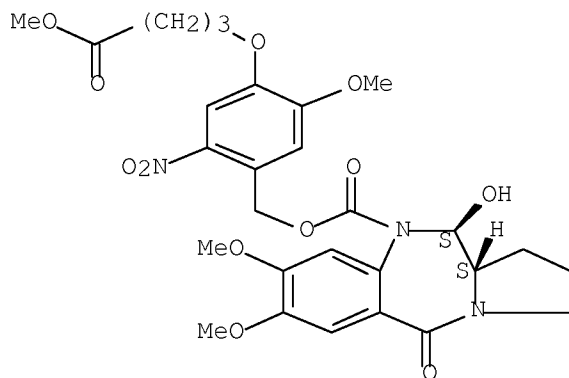


RN 848004-42-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,

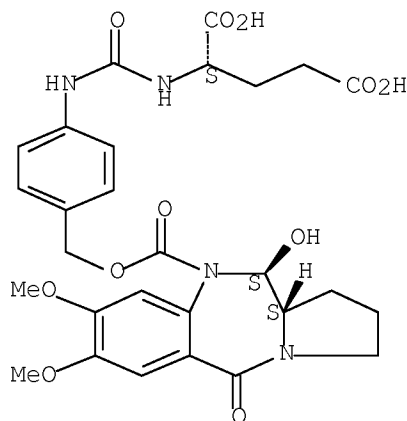
2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-,  
[5-methoxy-4-(4-methoxy-4-oxobutoxy)-2-nitrophenyl]methyl ester,  
(11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



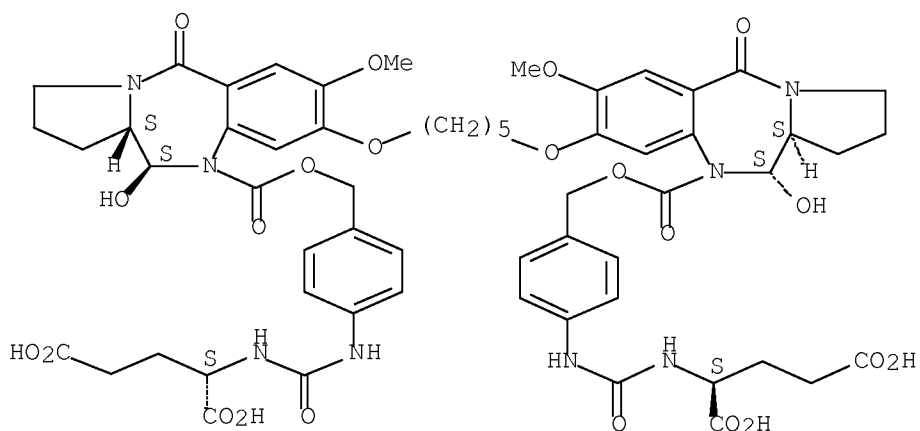
RN 848004-47-7 CAPLUS  
CN L-Glutamic acid, N-[[[4-[[[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-yl]carbonyl]oxy]methyl]phenyl]amino]carbonyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 848004-85-3 CAPLUS  
CN L-Glutamic acid, N,N'-[1,5-pentanediy]bis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneiminocarbonyl]]bis- (9CI)  
(CA INDEX NAME)

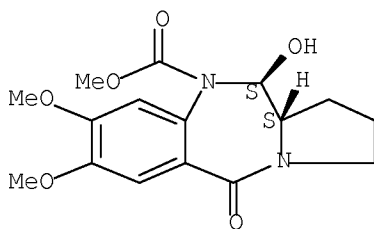
Absolute stereochemistry. Rotation (+).



RN 848005-01-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-, methyl ester,  
(11S,11aS)- (CA INDEX NAME)

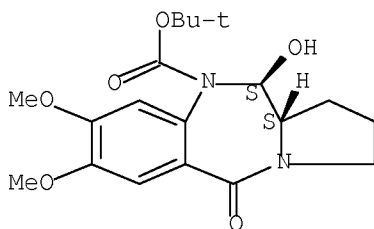
Absolute stereochemistry. Rotation (+).



RN 848005-02-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-, 1,1-dimethylethyl  
ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

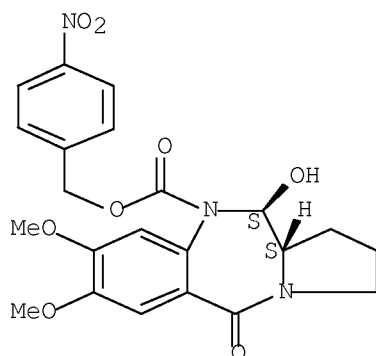


RN 848005-03-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,

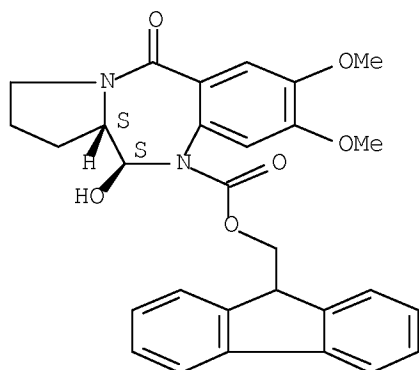
2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-,  
(4-nitrophenyl)methyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



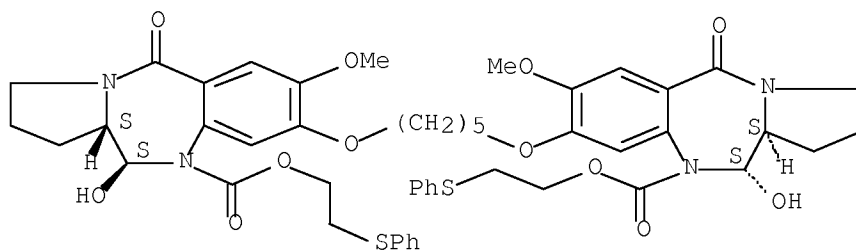
RN 848005-04-9 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-,  
9H-fluoren-9-ylmethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 848005-10-7 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,5-pentanediylobis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
methoxy-5-oxo-, bis[2-(phenylthio)ethyl] ester, (11S,11'S,11aS,11'aS)-  
(9CI) (CA INDEX NAME)

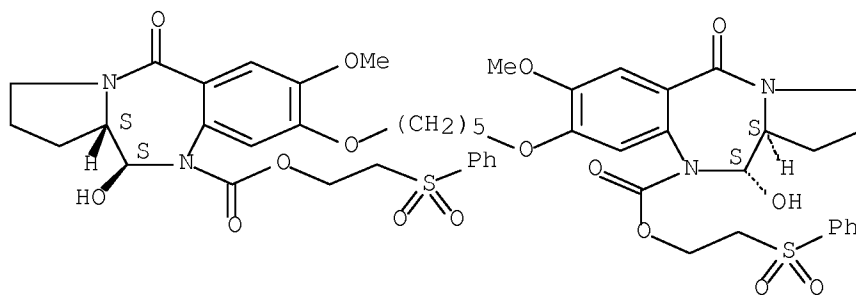
Absolute stereochemistry. Rotation (+).



RN 848005-11-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,5-pentanediy]bis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
methoxy-5-oxo-, bis[2-(phenylsulfonyl)ethyl] ester, (11S,11'S,11aS,11'aS)-  
(9CI) (CA INDEX NAME)

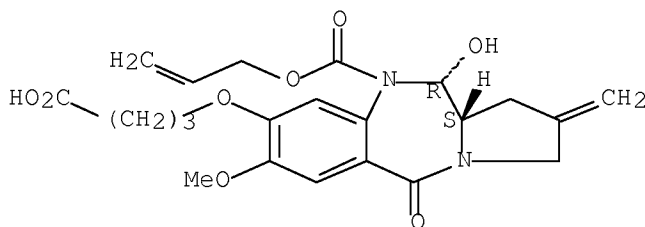
Absolute stereochemistry. Rotation (+).



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

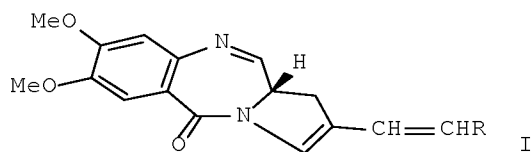
L11 ANSWER 14 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2004:908866 CAPLUS Full-text  
 DN 142:69572  
 TI Synthesis and Evaluation of a Triplex-Forming Oligonucleotide-Tomaymycin Conjugate  
 AU Zhilina, Zhanna V.; Ziemba, Amy J.; Trent, John O.; Reed, Michael W.; Gorn, Vladimir; Zhou, Qun; Duan, Wenhui; Hurley, Laurence; Ebbinghaus, Scot W.  
 CS Arizona Cancer Center, University of Arizona, Tucson, AZ, 85724-5024, USA  
 SO Bioconjugate Chemistry (2004), 15(6), 1182-1192  
 CODEN: BCCHE5; ISSN: 1043-1802  
 PB American Chemical Society  
 DT Journal  
 LA English  
 AB In most cases, unmodified oligonucleotides designed as antigene mols. are incapable of binding to DNA with sufficient stability to prevent gene expression. To stabilize binding to a polypurine tract in the HER-2/neu promoter, a triplex forming oligonucleotide (TFO) was conjugated to a pyrrolo[1,4]benzodiazepine (PBD), desmethyltomaymycin, and site-specific DNA binding was evaluated. An activated ester of the PBD moiety was conjugated by an acylation reaction to a free primary amine on a 50-atom aliphatic linker at the 5' end of the TFO. This long aliphatic linker was designed to provide a bridge from the major groove binding site of the TFO to the minor groove binding site of the PBD. Triplex formation by the resulting TFO-PBD conjugate occurred more slowly and with a nearly 30-fold lower affinity compared to an unconjugated TFO. PBD binding to the triplex target was demonstrated by protection from restriction enzyme digestion, and covalent binding to the exocyclic amino group of guanine was inferred by substituting specific guanines with inosines. Although the binding of the TFO was less efficient, this report demonstrates that in principle, TFOs can be used to direct the binding of a PBD to specific location. Further optimization of TFO-PBD conjugate design, likely involving optimization of the linker and perhaps placing a PBD at both ends of the TFO, will be needed to make gene modification robust.  
 IT 811798-00-2DP, conjugate with triplex-forming oligonucleotide  
 RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (synthesis of a triplex-forming oligonucleotide-tomaymycin conjugate and evaluation as a gene promoter targeting agent)  
 RN 811798-00-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(3-carboxypropoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, 10-(2-propen-1-yl) ester, (11R,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



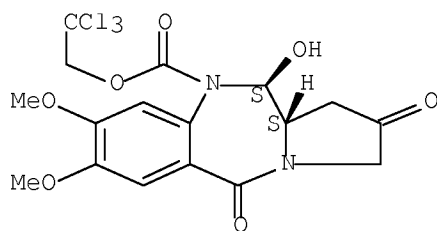
RE.CNT 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 15 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2004:189175 CAPLUS Full-text  
 DN 140:406790  
 TI A novel approach to the synthesis of cytotoxic C2-C3 unsaturated  
 pyrrolo[2,1-c]benzodiazepines (PBDs) with conjugated acrylyl  
 C2-substituents  
 AU Chen, Zhizhi; Gregson, Stephen J.; Howard, Philip W.; Thurston, David E.  
 CS Department of Pharmaceutical and Biological Chemistry, Cancer Research UK  
 Gene Targeted Drug Design Research Group, School of Pharmacy, London, WC1N  
 1AX, UK  
 SO Bioorganic & Medicinal Chemistry Letters (2004), 14(6), 1547-1549  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Science B.V.  
 DT Journal  
 LA English  
 OS CASREACT 140:406790  
 GI



AB A concise synthesis of three novel C2-C3 unsatd. pyrrolo[2,1-  
 c][1,4]benzodiazepine analogs I (R = CONMe<sub>2</sub>, CO<sub>2</sub>Me, CONH<sub>2</sub>) containing  
 conjugated acrylyl C2-substituents is reported that utilizes Heck coupling to  
 install the C2-acrylyl side chains. These analogs possess significant  
 cytotoxicity according to the NCI 60-cell line screen with I (R = CONMe<sub>2</sub>)  
 surpassing anthramycin in potency.  
 IT ~~689284-04-6P~~ ~~689284-05-7P~~ ~~689284-06-8P~~  
~~689284-07-9P~~ ~~689284-08-0P~~  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (preparation of cytotoxic C2-C3 unsatd. pyrrolo[2,1-c]benzodiazepines with  
 conjugated acrylyl C2-substituents)  
 RN 689284-04-6 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-2,5-dioxo-,  
 2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

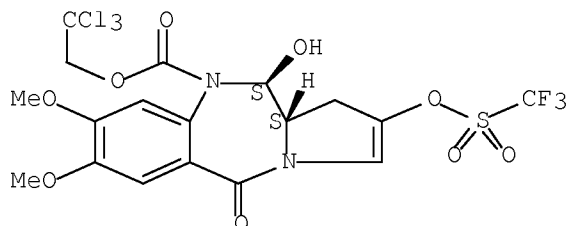




RN 689284-05-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
11,11a-dihydro-11-hydroxy-7,8-dimethoxy-5-oxo-2-  
[[trifluoromethyl)sulfonyl]oxy]-, 2,2,2-trichloroethyl ester, (11S,11aS)-  
(CA INDEX NAME)

Absolute stereochemistry.

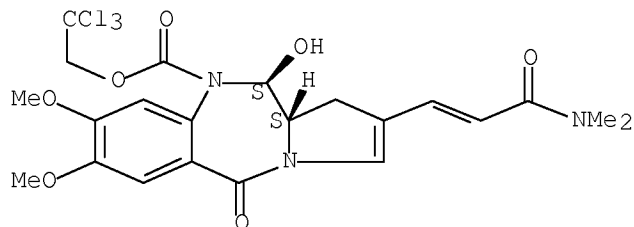


RN 689284-06-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2-[3-(dimethylamino)-3-oxo-1-propen-1-yl]-11,11a-dihydro-11-hydroxy-7,8-  
dimethoxy-5-oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

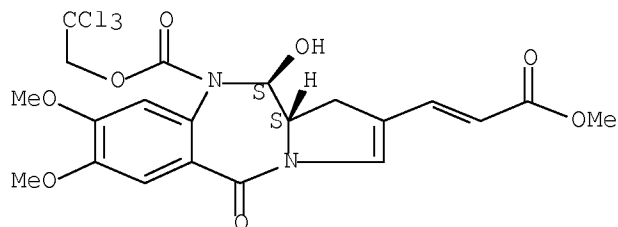


RN 689284-07-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
11,11a-dihydro-11-hydroxy-7,8-dimethoxy-2-(3-methoxy-3-oxo-1-propen-1-yl)-  
5-oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

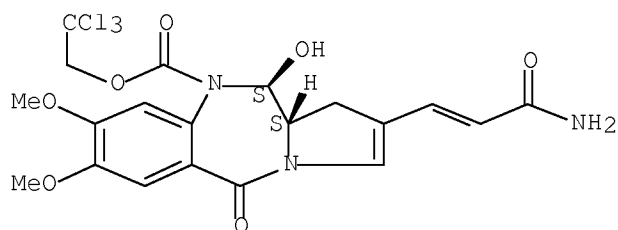


RN 689284-08-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2-(3-amino-3-oxo-1-propen-1-yl)-11,11a-dihydro-11-hydroxy-7,8-dimethoxy-5-  
oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

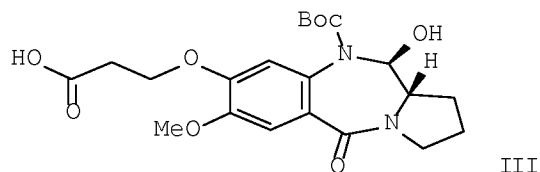
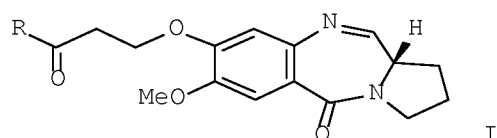
Absolute stereochemistry.

Double bond geometry unknown.



RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 16 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2004:99276 CAPLUS Full-text  
 DN 140:321339  
 TI Synthesis and biological evaluation of pyrrolo[2,1-c][1,4]benzodiazepine  
 (PBD) C8 cyclic amine conjugates  
 AU Masterson, Luke A.; Croker, Stephen J.; Jenkins, Terence C.; Howard,  
 Philip W.; Thurston, David E.  
 CS School of Pharmacy, Cancer Research UK Gene Targeted Drug Design Research  
 Group, University of London, London, WC1 1AX, UK  
 SO Bioorganic & Medicinal Chemistry Letters (2004), 14(4), 901-904  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Science B.V.  
 DT Journal  
 LA English  
 OS CASREACT 140:321339  
 GI



AB A series of pyrrolo[2,1-c][1,4]benzodiazepines I [R = (CH<sub>2</sub>)<sub>4</sub>N, (CH<sub>2</sub>)<sub>5</sub>N, 1-indoliny, 2-isindoliny (II)] were prepared from a common functionalized building block III that was conveniently synthesized on a large scale and in optically pure form. II was the most cytotoxic agent in this series, had the highest DNA-binding affinity, and showed significant activity in the in vivo hollow fiber assay.

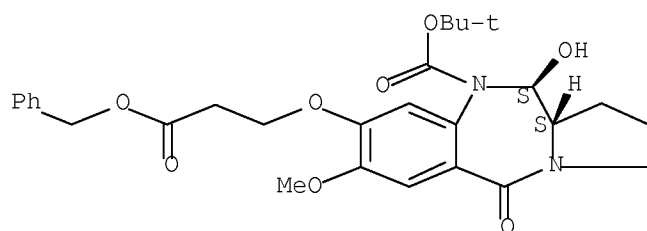
IT 679005-40-4P 679005-41-5P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(stereoselective preparation of N-Boc(carboxyethoxy)hydroxy(methoxy)pyrrolobenzodiazepinone via stereoselective oxidative heterocyclization of N-[(benzyloxycarbonylethoxy) (Boc-amino)methoxybenzoyl]pyrrolidinemethanol followed by debenzoylation)

RN 679005-40-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(phenylmethoxy)propoxy]-, 1,1-dimethylethyl ester, (11S,11aS)- (CA INDEX NAME)

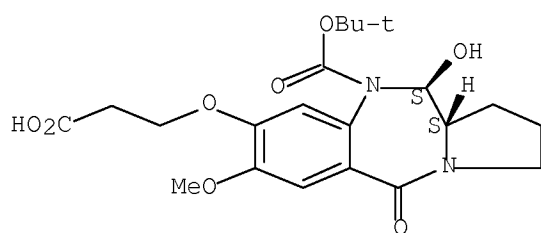
Absolute stereochemistry. Rotation (+).



RN 679005-41-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
10-(1,1-dimethylethyl) ester, (11S,11aS)- (CA INDEX NAME)

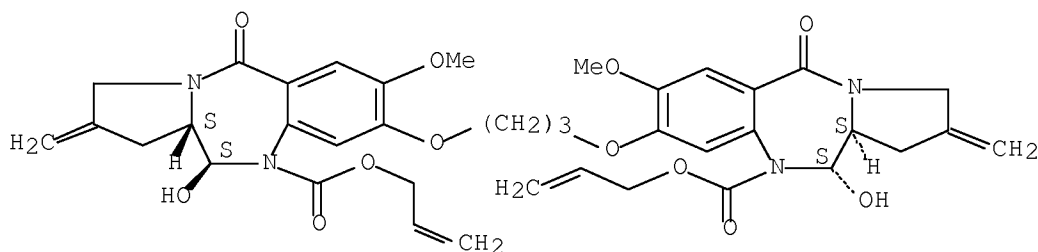
Absolute stereochemistry. Rotation (+).



RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 17 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2004:79123 CAPLUS Full-text  
 DN 140:280775  
 TI Linker Length Modulates DNA Cross-Linking Reactivity and Cytotoxic Potency of C8/C8' Ether-Linked C2-exo-Unsaturated Pyrrolo[2,1-c][1,4]benzodiazepine (PBD) Dimers  
 AU Gregson, Stephen J.; Howard, Philip W.; Gullick, Darren R.; Hamaguchi, Anzu; Corcoran, Kathryn E.; Brooks, Natalie A.; Hartley, John A.; Jenkins, Terence C.; Patel, Sejal; Guille, Matthew J.; Thurston, David E.  
 CS Cancer Research UK Gene Targeted Drug Design Research Group, The School of Pharmacy, University of London, London, WC1N 1AX, UK  
 SO Journal of Medicinal Chemistry (2004), 47(5), 1161-1174  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 140:280775  
 AB A C2/C2'-exo-unsatd. pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimer (DRG-16) with a C8-O(CH<sub>2</sub>)<sub>n</sub>O-C8' diether linkage (n = 5) has been synthesized that shows markedly superior in vitro cytotoxic potency (e.g., >3400-fold in IGROV1 ovarian cells) and interstrand DNA crosslinking reactivity (>10-fold) compared to the shorter homolog (SJG-136; n = 3). In contrast, for the C-ring unsubstituted series, the corresponding n = 5 dimer is generally less cytotoxic and has a lower interstrand crosslinking reactivity compared to its shorter n = 3 homolog. Dimer DRG-16 cross-links DNA with >10-fold efficiency compared to 4a, and also inhibits the activity of the restriction endonuclease BamH1 more efficiently. The C2-exo-unsatd. PBD dimers 4a,b are not only more effective than their C-ring saturated counterparts in terms of induced ΔT<sub>m</sub> shift, but they also exert this effect more rapidly. Mol. modeling shows a rank order of DRG-16 (n = 5) > SJG-136 (n = 3) in terms of binding energy toward duplexes containing embedded target 5'-GAT1-2C cross-link sequences, reflecting the superior fit of the C2-exo-unsatd. rather than saturated C-rings of the PBD dimers. A novel synthesis of core synthetic building blocks for PBD dimers via stepwise Mitsunobu reaction and nitration with Cu(NO<sub>3</sub>)<sub>2</sub> is also reported.  
 IT 232931-64-5P 260418-31-3P  
 RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (linker length modulates DNA crosslinking reactivity and cytotoxic potency of C8/C8' ether-linked C2-exo-unsatd. pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimers)  
 RN 232931-64-5 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

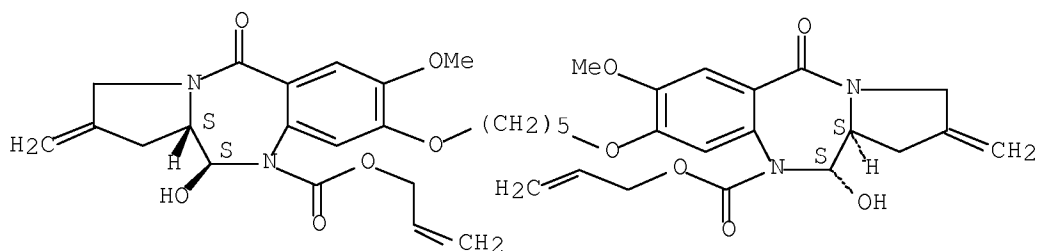
Absolute stereochemistry.



RN 260418-31-3 CAPLUS

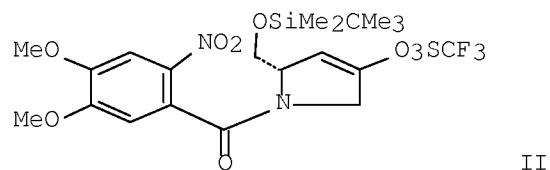
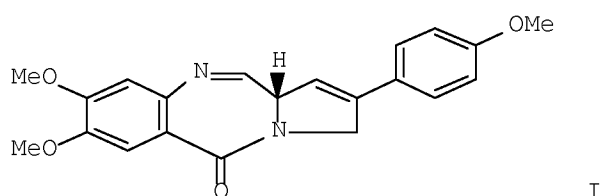
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,5-pentanediy]bis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-  
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



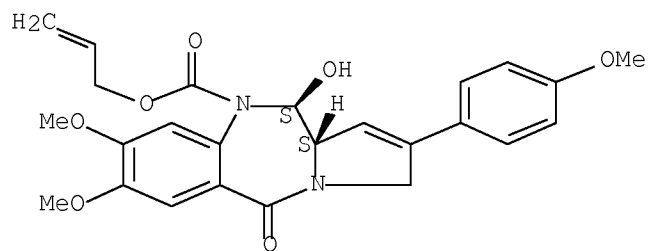
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 18 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2003:496748 CAPLUS Full-text  
 DN 140:42146  
 TI Synthesis of a novel C2-aryl substituted 1,2-unsaturated  
 pyrrolobenzodiazepine  
 AU Kang, Gyoung-Dong; Howard, Philip W.; Thurston, David E.  
 CS Cancer Research UK Gene Targeted Drug Design Research Group, The School of  
 Pharmacy, University of London, London, WC1N 1AX, UK  
 SO Chemical Communications (Cambridge, United Kingdom) (2003), (14),  
 1688-1689  
 CODEN: CHCOFS; ISSN: 1359-7345  
 PB Royal Society of Chemistry  
 DT Journal  
 LA English  
 OS CASREACT 140:42146  
 GI



AB The pyrrolobenzodiazepine I was prepared via the enol triflate intermediate  
 II. The regiochem. of triflation is dependent upon the point at which the  
 reaction is performed during the synthetic route.  
 IT 637035-48-4P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (preparation of an aryl-substituted 1,2-unsatd. pyrrolobenzodiazepine)  
 RN 637035-48-4 CAPLUS  
 CN 3H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 11,11a-dihydro-11-hydroxy-7,8-dimethoxy-2-(4-methoxyphenyl)-5-oxo-,  
 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

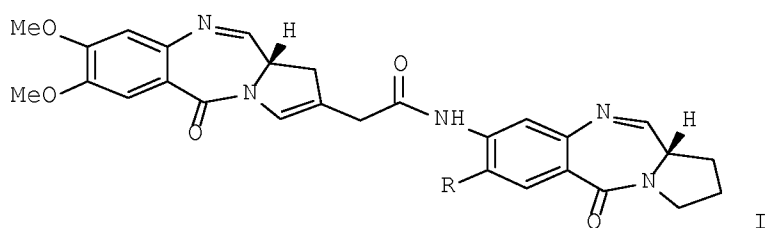
Absolute stereochemistry.



RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

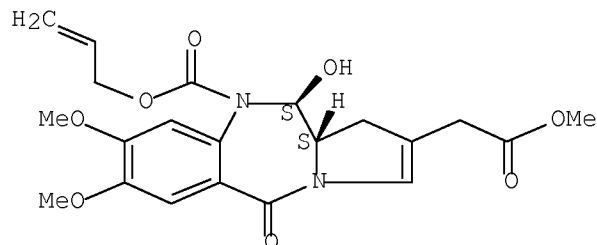


L11 ANSWER 19 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2003:485873 CAPLUS Full-text  
 DN 139:261068  
 TI Synthesis of the first examples of A-C8/C-C2 amide-Linked  
 pyrrolo[2,1-c][1,4]benzodiazepine dimers  
 AU Gregson, Stephen J.; Howard, Philip W.; Thurston, David E.  
 CS The School of Pharmacy, Cancer Research UK Gene Targeted Drug Design  
 Research Group, University of London, London, WC1N 1AX, UK  
 SO Bioorganic & Medicinal Chemistry Letters (2003), 13(14), 2277-2280  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Science B.V.  
 DT Journal  
 LA English  
 OS CASREACT 139:261068  
 GI



AB The novel A-C8/C-C2 amide-linked pyrrolo[2,1-c][1,4]benzodiazepine dimers I (R = H, MeO) were prepared via a convergent routes. These compds. lack the potent DNA interstrand crosslinking ability and resultant pronounced cytotoxicity of the known A-C8/A-C8' linked dimers.  
 IT 260417-92-3  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (synthesis of first examples of A-C8/C-C2 amide-Linked pyrrolo[2,1-c][1,4]benzodiazepine dimers)  
 RN 260417-92-3 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acetic acid, 5,10,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-10-[(2-propenyloxy)carbonyl]-, methyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 600713-78-8P 600713-79-9P 600713-84-6P  
 600713-85-7P 600713-86-8P 600713-87-9P  
 600713-88-0P

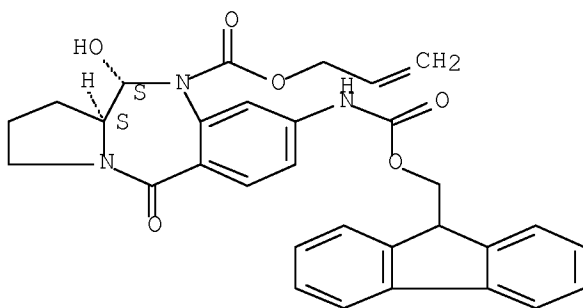
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(synthesis of first examples of A-C8/C-C2 amide-Linked pyrrolo[2,1-c][1,4]benzodiazepine dimers)

RN 600713-78-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-2,3,11,11a-tetrahydro-11-hydroxy-5-oxo-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

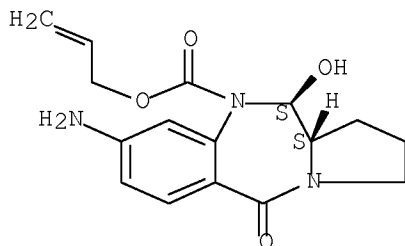
Absolute stereochemistry.



RN 600713-79-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-amino-2,3,11,11a-tetrahydro-11-hydroxy-5-oxo-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

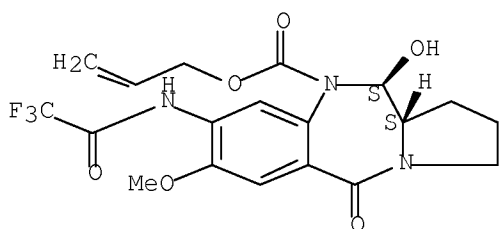
Absolute stereochemistry.



RN 600713-84-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[(2,2,2-trifluoroacetyl)amino]-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

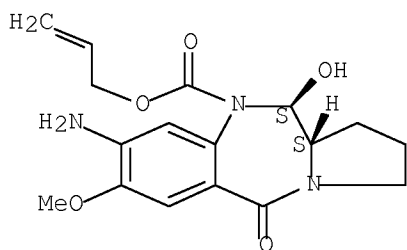
Absolute stereochemistry.



RN 600713-85-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-amino-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2-propen-1-yl  
ester, (11S,11aS)- (CA INDEX NAME)

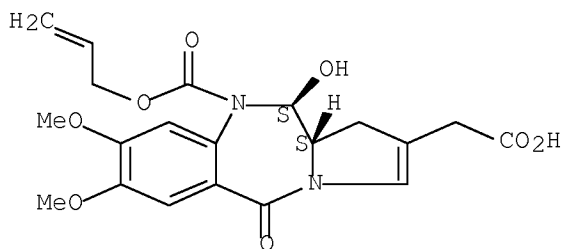
Absolute stereochemistry.



RN 600713-86-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acetic acid, 5,10,11,11a-tetrahydro-  
11-hydroxy-7,8-dimethoxy-5-oxo-10-[(2-propen-1-yloxy)carbonyl]-,  
(11S,11aS)- (CA INDEX NAME)

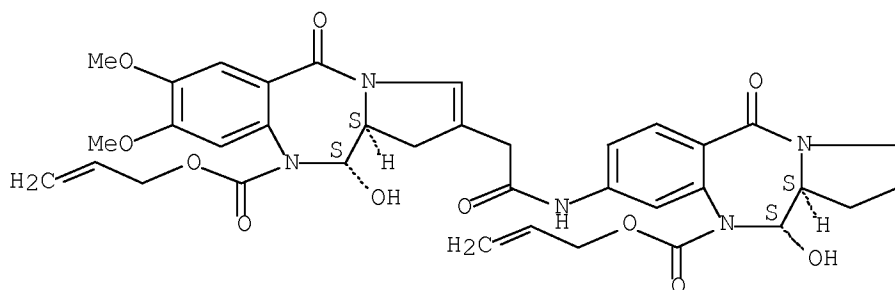
Absolute stereochemistry.



RN 600713-87-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2-[2-[[[(11S,11aS)-2,3,5,10,11,11a-hexahydro-11-hydroxy-5-oxo-10-[(2-propen-  
1-yloxy)carbonyl]-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]amino]-2-  
oxoethyl]-11,11a-dihydro-11-hydroxy-7,8-dimethoxy-5-oxo-, 2-propen-1-yl  
ester, (11S,11aS)- (CA INDEX NAME)

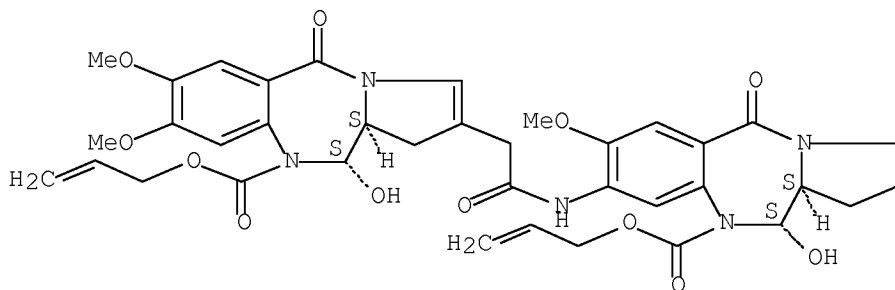
Absolute stereochemistry.



RN 600713-88-0 CAPLUS

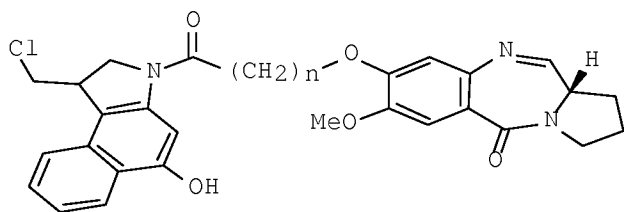
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2-[2-[[ (11S,11aS)-2,3,5,10,11,11a-hexahydro-11-hydroxy-7-methoxy-5-oxo-10-  
[(2-propen-1-yloxy)carbonyl]-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-  
yl]amino]-2-oxoethyl]-11,11a-dihydro-11-hydroxy-7,8-dimethoxy-5-oxo-,  
2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 20 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2003:323970 CAPLUS Full-text  
 DN 139:69239  
 TI Unsymmetrical DNA Cross-Linking Agents: Combination of the CBI and PBD Pharmacophores  
 AU Tercel, Moana; Stribbling, Stephen M.; Sheppard, Hilary; Siim, Bronwyn G.; Wu, Kent; Pullen, Susan M.; Botting, K. Jane; Wilson, William R.; Denny, William A.  
 CS Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, University of Auckland, Auckland, 92019, N. Z.  
 SO Journal of Medicinal Chemistry (2003), 46(11), 2132-2151  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 139:69239  
 GI



I

AB A set of chiral amides I ( $n = 1 - 5$ ), each combining the seco-1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol-4-one (seco-CBI) and pyrrolo[2,1-c][1,4]benzodiazepine (PBD) pharmacophores, was designed and prepared. I were anticipated to cross-link between N3 of adenine and N2 of guanine in the minor groove of DNA. The compds., which differ in the chain length separating the two alkylation subunits, and the configuration of the CBI portion, showed great variation in cellular toxicity (over 4 orders of magnitude in a cell line panel) with the most potent example exhibiting IC<sub>50</sub>s in the pM range. Cytotoxicity correlated with the ability of I to cross-link naked DNA. Crosslinking was also observed in living cells, at much lower concns. than for a related sym. PBD dimer. A thermal cleavage assay was used to assess sequence selectivity, demonstrating that the CBI portion controlled the alkylation sites, while the PBD substituent increased the overall efficiency of alkylation. Several compds. were tested for in vivo activity using a tumor growth delay assay against WiDr human colon carcinoma xenografts, with (S,S)-I ( $n = 5$ ) (the most cytotoxic and most efficient cross-linker) showing a statistically significant increase in survival time following a single iv dose.

IT 550355-98-1P 550356-00-8P 550356-02-0P  
 550356-04-2P 550356-06-4P 550356-07-5P  
 550356-08-6P 550356-09-7P 550356-19-9P  
 550356-20-2P 550356-21-3P 550356-22-4P  
 550356-23-5P 550356-24-6P 550356-25-7P  
 550356-26-8P 550356-27-9P 550356-28-0P  
 550356-29-1P 550356-30-4P 550356-47-3P  
 550356-50-8P 550356-53-1P

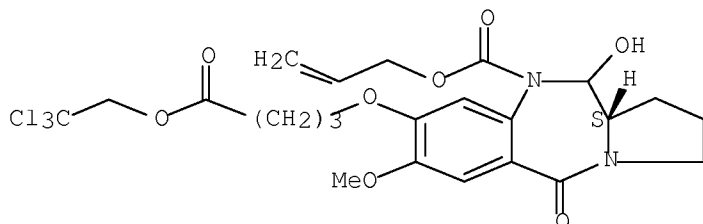
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of chiral (dihydrobenzindolyl)oxoalkoxy pyrrolodiazepinones as unsym. DNA crosslinking and antitumor agents)

RN 550355-98-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[4-oxo-4-(2,2,2-trichloroethoxy)butoxy]-, 2-propenyl ester, (11aS)- (9CI) (CA INDEX NAME)

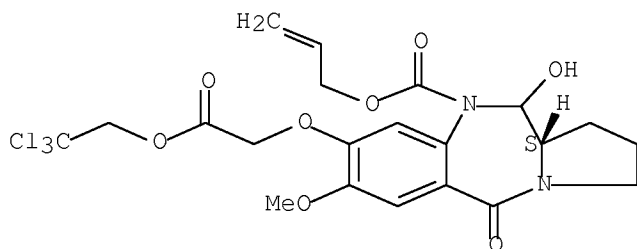
Absolute stereochemistry.



RN 550356-00-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[2-oxo-2-(2,2,2-trichloroethoxy)ethoxy]-, 2-propenyl ester, (11aS)- (9CI) (CA INDEX NAME)

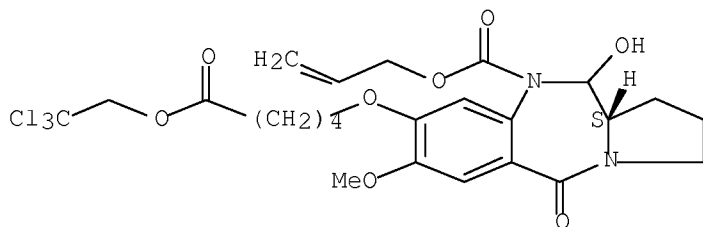
Absolute stereochemistry.



RN 550356-02-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[[5-oxo-5-(2,2,2-trichloroethoxy)pentyl]oxy]-, 2-propenyl ester, (11aS)- (9CI) (CA INDEX NAME)

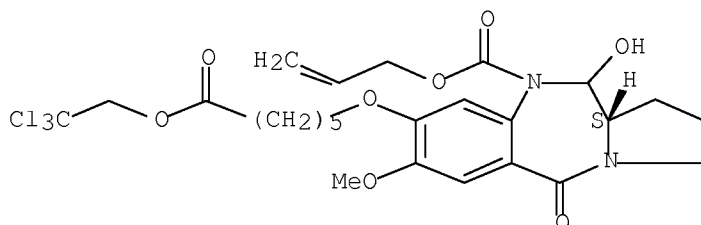
Absolute stereochemistry.



RN 550356-04-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[6-oxo-6-(2,2,2-  
trichloroethoxy)hexyl]oxy]-, 2-propenyl ester, (11aS)- (9CI) (CA INDEX  
NAME)

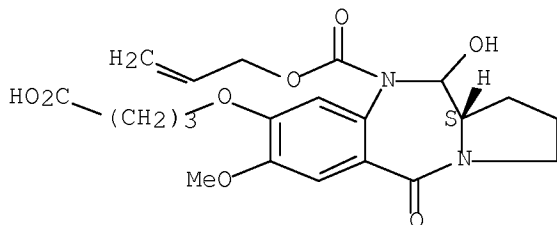
Absolute stereochemistry.



RN 550356-06-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(3-carboxypropoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
10-(2-propenyl) ester, (11aS)-(9CI) (CA INDEX NAME)

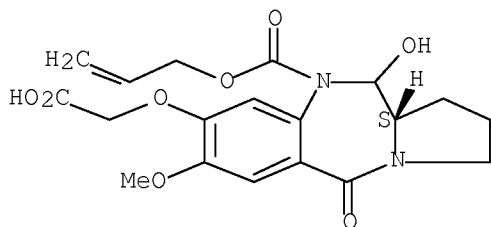
Absolute stereochemistry.



RN 550356-07-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(carboxymethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
10-(2-propenyl) ester, (11aS)- (9CI) (CA INDEX NAME)

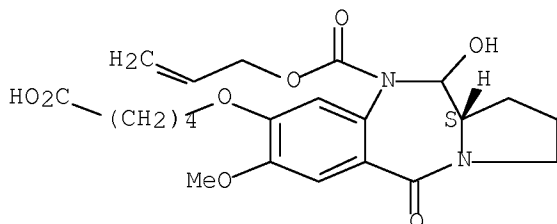
Absolute stereochemistry.



RN 550356-08-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(4-carboxybutoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
10-(2-propenyl) ester, (11aS)- (9CI) (CA INDEX NAME)

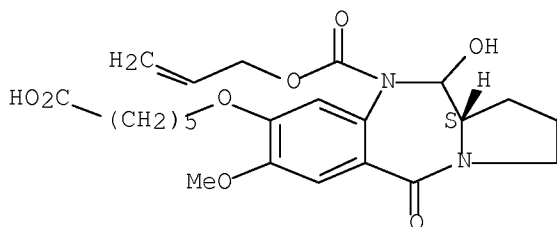
Absolute stereochemistry.



RN 550356-09-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[(5-carboxypentyl)oxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-  
, 10-(2-propenyl) ester, (11aS)- (9CI) (CA INDEX NAME)

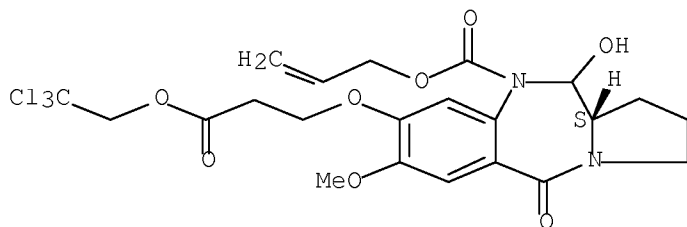
Absolute stereochemistry.



RN 550356-19-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2,2,2-  
trichloroethoxy)propoxy]-, 2-propenyl ester, (11aS)- (9CI) (CA INDEX  
NAME)

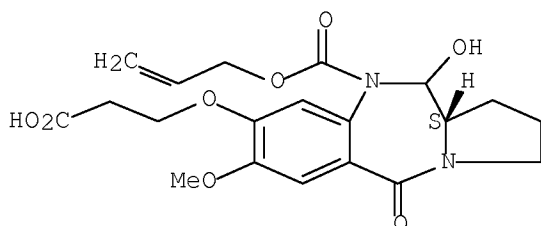
Absolute stereochemistry.





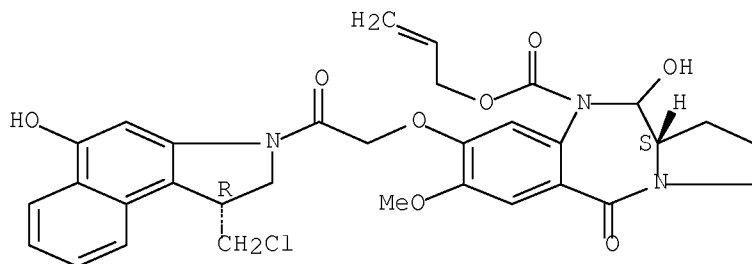
RN 550356-20-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
 10-(2-propenyl) ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



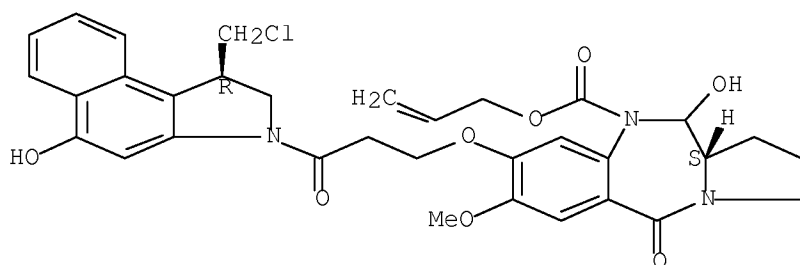
RN 550356-21-3 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-[2-[(1R)-1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]-2-oxoethoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2-propenyl  
 ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 550356-22-4 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-[3-[(1R)-1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2-propenyl  
 ester, (11aS)- (9CI) (CA INDEX NAME)

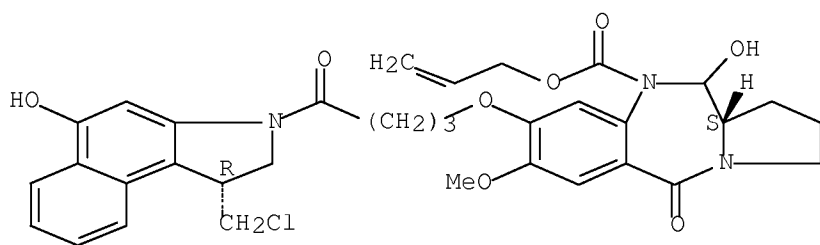
Absolute stereochemistry.



RN 550356-23-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[4-[(1R)-1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]-4-oxobutoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2-propenyl ester, (11aS)- (9CI) (CA INDEX NAME)

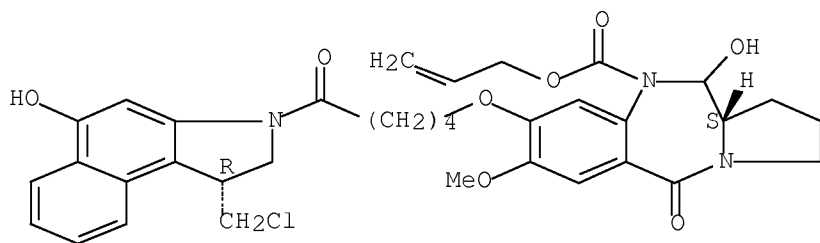
Absolute stereochemistry.



RN 550356-24-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[[5-[(1R)-1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]-5-oxopentyl]oxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2-propenyl ester, (11aS)- (9CI) (CA INDEX NAME)

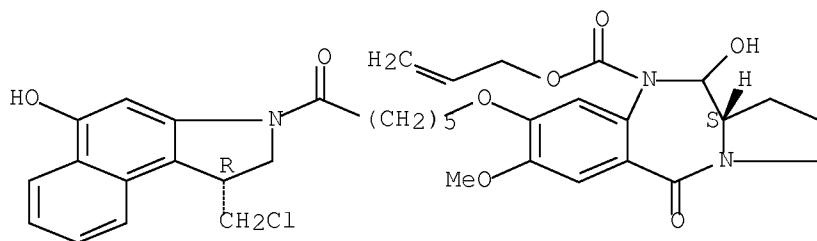
Absolute stereochemistry.



RN 550356-25-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[[6-[(1R)-1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]-6-oxohexyl]oxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2-propenyl ester, (11aS)- (9CI) (CA INDEX NAME)

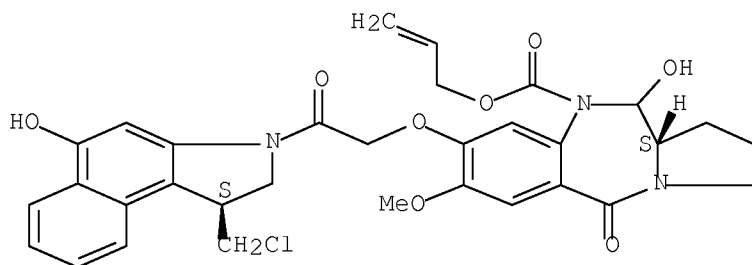
Absolute stereochemistry.



RN 550356-26-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[2-[(1S)-1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]-2-oxoethoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2-propenyl ester, (11aS)- (9CI) (CA INDEX NAME)

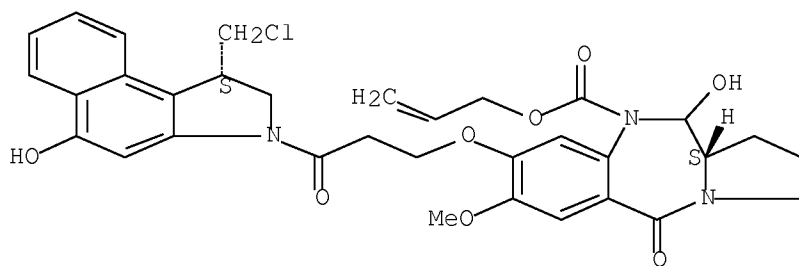
Absolute stereochemistry.



RN 550356-27-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[3-[(1S)-1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2-propenyl ester, (11aS)- (9CI) (CA INDEX NAME)

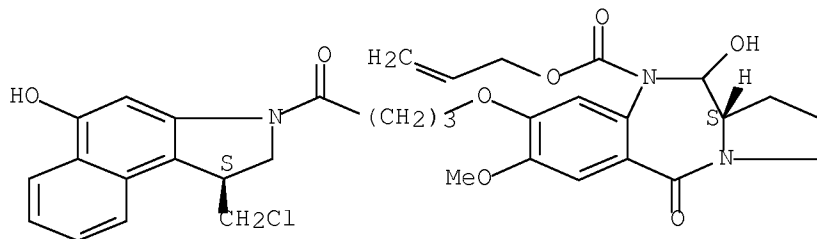
Absolute stereochemistry.



RN 550356-28-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[4-[(1S)-1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]-4-oxobutoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2-propenyl ester, (11aS)- (9CI) (CA INDEX NAME)

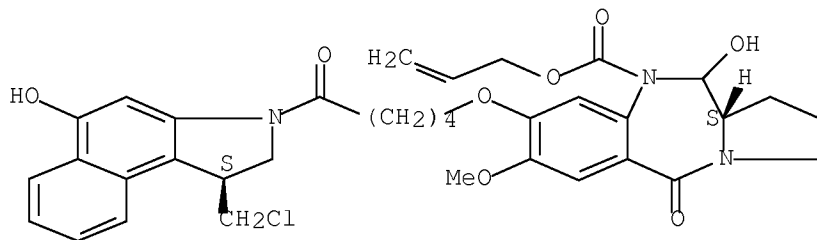
Absolute stereochemistry.



RN 550356-29-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[[5-[(1S)-1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]-5-oxopentyl]oxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2-propenyl ester, (11aS)- (9CI) (CA INDEX NAME)

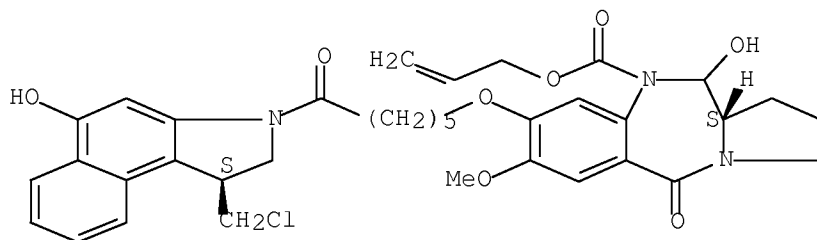
Absolute stereochemistry.



RN 550356-30-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[[6-[(1S)-1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]-6-oxohexyl]oxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2-propenyl ester, (11aS)- (9CI) (CA INDEX NAME)

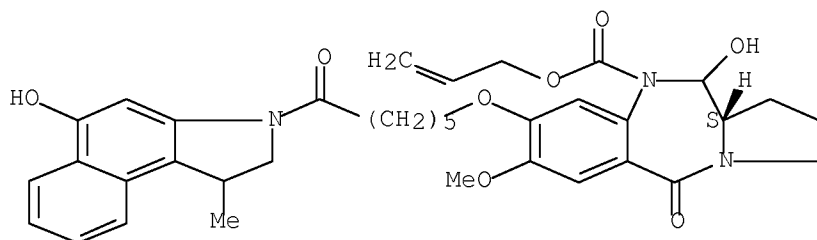
Absolute stereochemistry.



RN 550356-47-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[[6-(1,2-dihydro-5-hydroxy-1-methyl-3H-benz[e]indol-3-yl)-6-  
oxohexyl]oxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
2-propenyl ester, (11aS)- (9CI) (CA INDEX NAME)

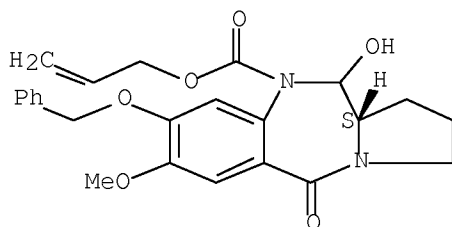
Absolute stereochemistry.



RN 550356-50-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-,  
2-propenyl ester, (11aS)- (9CI) (CA INDEX NAME)

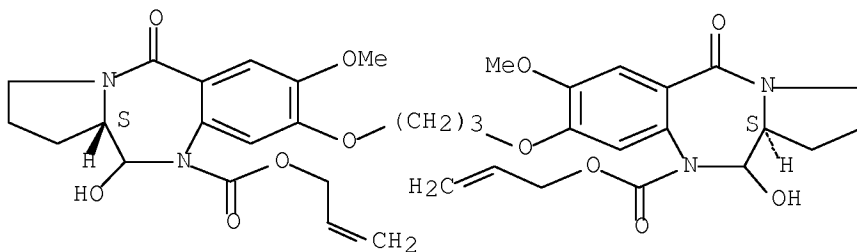
Absolute stereochemistry.



RN 550356-53-1 CAPLUS

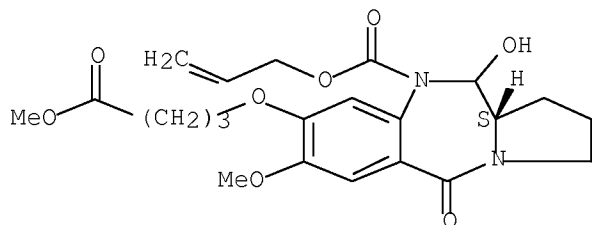
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
methoxy-5-oxo-, di-2-propenyl ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



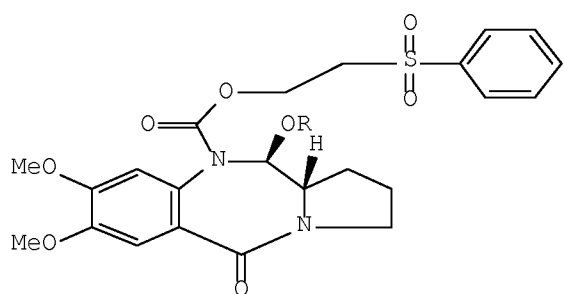
IT 550356-10-0P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of chiral (dihydrobenzindolyl)oxoalkoxy pyrrolodiazepinones as  
 unsym. DNA crosslinking and antitumor agents)  
 RN 550356-10-0 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(4-methoxy-4-oxobutoxy)-5-oxo-  
 , 2-propenyl ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

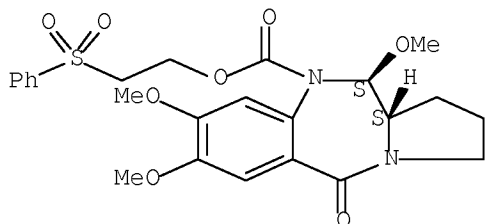
L11 ANSWER 21 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2002:324912 CAPLUS Full-text  
 DN 137:247674  
 TI Synthesis and biological evaluation of an N10-Psec substituted  
 pyrrolo[2,1-c][1,4]benzodiazepine prodrug  
 AU Berry, Jane M.; Howard, Philip W.; Kelland, Lloyd R.; Thurston, David E.  
 CS CRUK Gene Targeted Drug Design Research Group, Cancer Research  
 Laboratories, School of Pharmaceutical Sciences, University of Nottingham,  
 Nottingham, NG7 2RD, UK  
 SO Bioorganic & Medicinal Chemistry Letters (2002), 12(10), 1413-1416  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Science Ltd.  
 DT Journal  
 LA English  
 OS CASREACT 137:247674  
 GI



I

AB The first example of an N10-protected [e.g., Psec, I (R = H, Me)] pyrrolo[2,1-  
 c][1,4]benzodiazepine (PBD) analog that retains significant cytotoxicity in a  
 number of tumor cell lines is reported.  
 IT 260391-46-6P 260391-47-7P 260391-48-8P  
 461462-59-9P  
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic  
 preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant  
 or reagent)  
 (preparation and antitumor activity of pyrrolobenzodiazepines)  
 RN 260391-46-6 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-7,8,11-trimethoxy-5-oxo-, 2-(phenylsulfonyl)ethyl  
 ester, (11S,11aS)- (CA INDEX NAME)

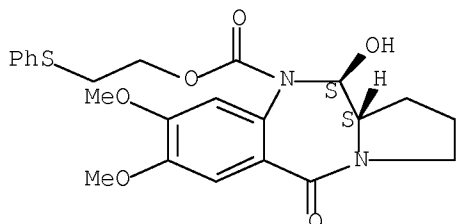
Absolute stereochemistry.



RN 260391-47-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-, 2-(phenylthio)ethyl  
ester, (11S,11aS)- (CA INDEX NAME)

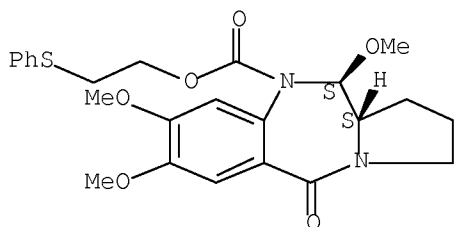
Absolute stereochemistry.



RN 260391-48-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7,8,11-trimethoxy-5-oxo-, 2-(phenylthio)ethyl ester,  
(11S,11aS)- (CA INDEX NAME)

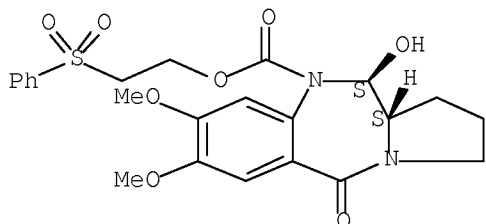
Absolute stereochemistry.



RN 461462-59-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-,  
2-(phenylsulfonyl)ethyl ester, (11S,11aS)- (CA INDEX NAME)

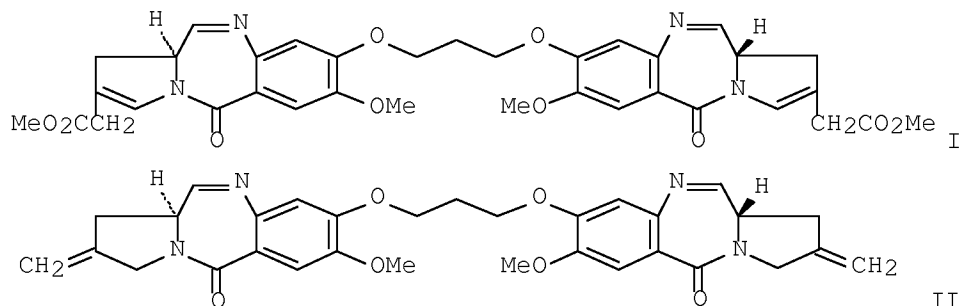
Absolute stereochemistry. Rotation (+).



RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

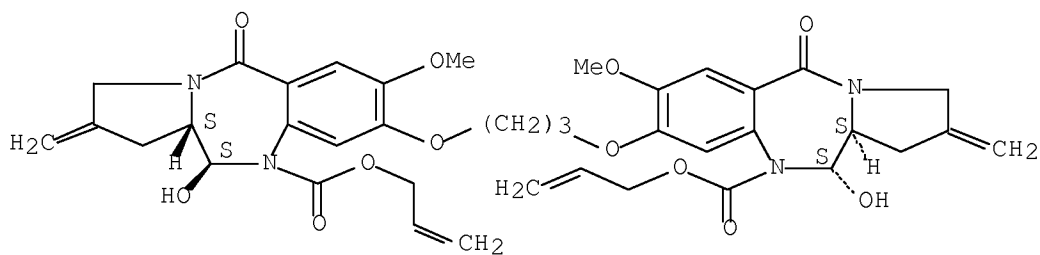


L11 ANSWER 22 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2001:746612 CAPLUS Full-text  
 DN 136:200170  
 TI Synthesis of the first example of a C2-C3/C2'-C3'-endo unsaturated  
 pyrrolo[2,1-c][1,4]benzodiazepine dimer  
 AU Gregson, S. J.; Howard, P. W.; Corcoran, K. E.; Jenkins, T. C.; Kelland,  
 L. R.; Thurston, D. E.  
 CS Cancer Research Laboratories, CRC Gene Targeted Drug Design Research  
 Group, University of Nottingham, School of Pharmaceutical Sciences,  
 Nottingham, NG7 2RD, UK  
 SO Bioorganic & Medicinal Chemistry Letters (2001), 11(21), 2859-2862  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Science Ltd.  
 DT Journal  
 LA English  
 OS CASREACT 136:200170  
 GI



AB We report the first example of a C2-C3/C2'-C3'-endo unsatd. pyrrolo[2,1-  
 c][1,4]benzodiazepine (PBD) dimer (I) synthesized through a new and efficient  
 route, thus establishing that C2-C3-endo unsatn. enhances both cytotoxicity  
 and DNA-binding affinity in A-ring-linked PBD dimers but to a lesser extent  
 than C2/C2'-exo-unsatn. This new route has allowed the preparation of  
 multigram quantities of the related clin. candidate II and should lead to more  
 structurally diverse PBD dimer analogs.  
 IT 232931-64-5P 260418-01-7P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (preparation of first example of C2-C3/C2'-C3'-endo unsatd.  
 pyrrolo[2,1-c][1,4]benzodiazepine dimer)  
 RN 232931-64-5 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
 methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-  
 (9CI) (CA INDEX NAME)

Absolute stereochemistry.

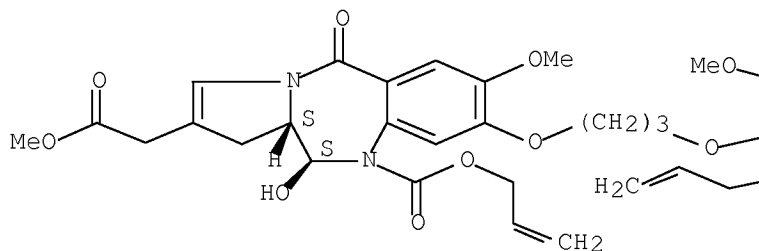


RN 260418-01-7 CAPLUS

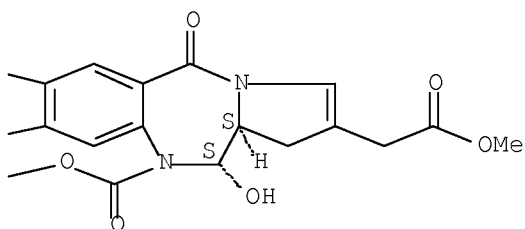
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acetic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[5,10,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-10-[(2-propenyloxy)carbonyl]-, dimethyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

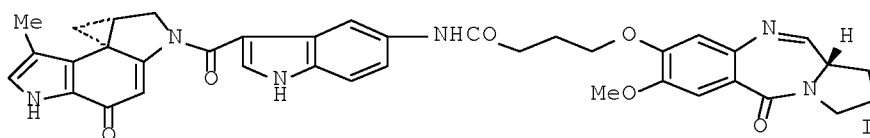


PAGE 1-B



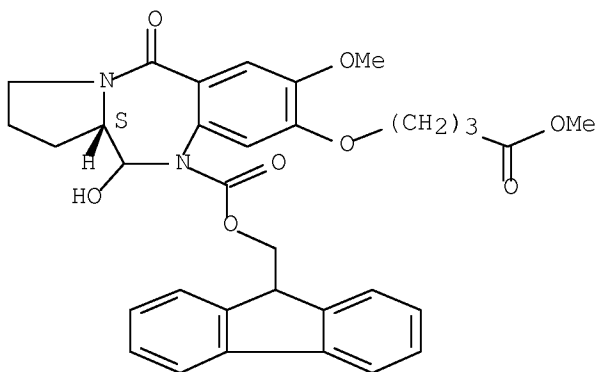
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 23 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2001:304925 CAPLUS Full-text  
 DN 135:107180  
 TI Design and Synthesis of a Novel DNA-DNA Interstrand Adenine-Guanine  
 Cross-Linking Agent  
 AU Zhou, Qun; Duan, Wenhui; Simmons, Denise; Shayo, Yuda; Raymond, Mary Ann;  
 Dorr, Robert T.; Hurley, Laurence H.  
 CS Arizona Cancer Center, Tucson, AZ, 85724, USA  
 SO Journal of the American Chemical Society (2001), 123(20), 4865-4866  
 CODEN: JACSAT; ISSN: 0002-7863  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 135:107180  
 GI



AB The heterobifunctional compound UTA-6026 (I) that forms interstrand cross  
 linking between adenine and guanine six base pairs apart was designed and  
 synthesized in 10 steps starting from vanillic acid in 6% overall yield. It  
 shows mixed sequence-specific alkylation selectivity and demonstrates potent  
 antitumor activity against several tumor cell lines.  
 IT 349536-28-3P 349536-29-4P 349536-30-7P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (design and synthesis of a novel DNA-DNA interstrand adenine-guanine  
 crosslinking agent)  
 RN 349536-28-3 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(4-methoxy-4-oxobutoxy)-5-oxo-  
 , 9H-fluorene-9-ylmethyl ester, (11aS)- (CA INDEX NAME)

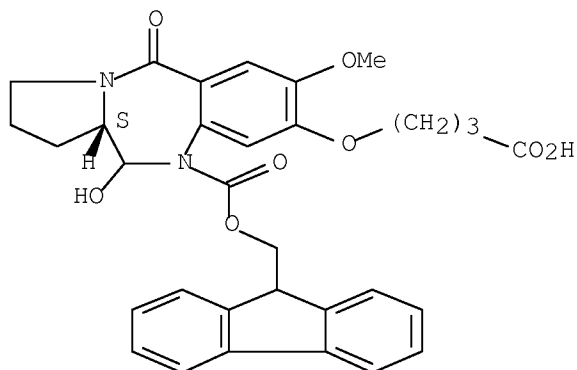
Absolute stereochemistry.



RN 349536-29-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(3-carboxypropoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
10-(9H-fluoren-9-ylmethyl) ester, (11aS)- (CA INDEX NAME)

Absolute stereochemistry.

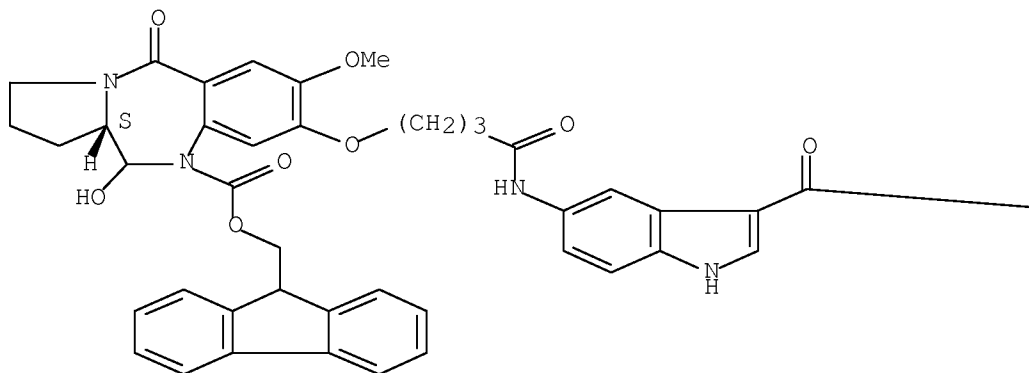


RN 349536-30-7 CAPLUS

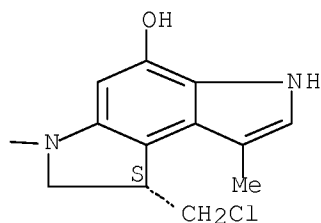
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[4-[[3-[[[(1S)-1-(chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-  
b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl]amino]-4-oxobutoxy]-  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 9H-fluoren-9-ylmethyl  
ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



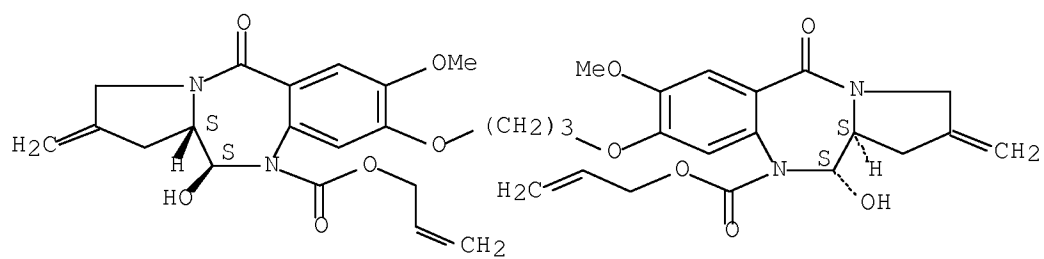
PAGE 1-B



RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 24 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2001:68712 CAPLUS Full-text  
 DN 134:260871  
 TI Design, synthesis, and evaluation of a novel pyrrolobenzodiazepine  
 DNA-interactive agent with highly efficient cross-linking ability and  
 potent cytotoxicity  
 AU Gregson, Stephen J.; Howard, Philip W.; Hartley, John A.; Brooks, Natalie  
 A.; Adams, Lesley J.; Jenkins, Terence C.; Kelland, Lloyd R.; Thurston,  
 David E.  
 CS CRC Gene Targeted Drug Design Research Group, Cancer Research Laboratories  
 University of Nottingham, Nottingham, NG7 2RD, UK  
 SO Journal of Medicinal Chemistry (2001), 44(5), 737-748  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 134:260871  
 AB A novel sequence-selective pyrrolobenzodiazepine (PBD) dimer 5 (SJG-136) has  
 been developed that comprises two C2-exo-methylene-substituted DC-81 (3)  
 subunits tethered through their C8 positions via an inert propanedioxy linker.  
 This sym. mol. is a highly efficient minor groove interstrand DNA crosslinking  
 agent (XL50 = 0.045  $\mu$ M) that is 440-fold more potent than melphalan. Thermal  
 denaturation studies show that, after 18 h incubation with calf thymus DNA at  
 a 5:1 DNA/ligand ratio, it increases the T<sub>m</sub> value by 33.6°, the highest value  
 so far recorded in this assay. The analogous dimer 4 (DSB-120) that lacks  
 substitution/unsatn. at the C2 position elevates melting by only 15.1° under  
 the same conditions, illustrating the effect of introducing C2-exo-unsatn.  
 which serves to flatten the C-rings and achieve a superior isohelical fit  
 within the DNA minor groove. This behavior is supported by mol. modeling  
 studies which indicate that (i) the PBD units are covalently bonded to  
 guanines on opposite strands to form a cross-link, (ii) 5 has a greater  
 binding energy compared to 4, and (iii) 4 and 5 have equivalent binding sites  
 that span six base pairs. Dimer 5 is significantly more cytotoxic than 4 in a  
 number of human ovarian cancer cell lines (e.g., IC<sub>50</sub> values of 0.0225 nM vs.  
 7.2 nM, resp., in A2780 cells). Furthermore, it retains full potency in the  
 cisplatin-resistant cell line A2780cisR (0.024 nM), whereas 4 loses activity  
 (0.21  $\mu$ M) with a resistance factor of 29.2. This may be due to a lower level  
 of inactivation of 5 by intracellular thiol-containing mols. A dilactam  
 analog, tetralactam of 5 that lacks the electrophilic N10-C11/N10'-C11' imine  
 moieties has also been synthesized and evaluated. Although unable to interact  
 covalently with DNA, tetralactam still stabilizes the helix ( $\Delta$ T<sub>m</sub> = 0.78°) and  
 has significant cytotoxicity in some cell lines (i.e., IC<sub>50</sub> = 0.57  $\mu$ M in CH1  
 cells), presumably exerting its effect through noncovalent interaction with  
 DNA.  
 IT 232931-64-5P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (design, synthesis, and evaluation of a novel pyrrolobenzodiazepine  
 DNA-interactive agent with highly efficient crosslinking ability and  
 potent cytotoxicity)  
 RN 232931-64-5 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
 methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-  
 (9CI) (CA INDEX NAME)

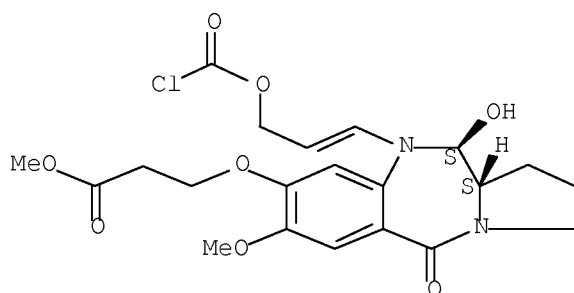
Absolute stereochemistry.



RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

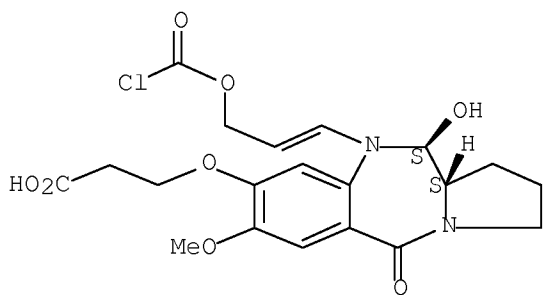
L11 ANSWER 25 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2000:787600 CAPLUS Full-text  
 DN 134:95090  
 TI Pyrrolo[2,1-c][1,4]benzodiazepine (PBD)-distamycin hybrid inhibits DNA binding to transcription factor Sp1  
 AU Baraldi, P. G.; Cacciari, B.; Guiotto, A.; Romagnoli, R.; Spalluto, G.; Leoni, A.; Bianchi, N.; Feriotto, G.; Rutigliano, C.; Mischiati, C.; Gambari, Roberto  
 CS Dipartimento di Scienze Farmaceutiche, Universita di Ferrara, Ferrara, 44100, Italy  
 SO Nucleosides, Nucleotides & Nucleic Acids (2000), 19(8), 1219-1229  
 CODEN: NNNAFY; ISSN: 1525-7770  
 PB Marcel Dekker, Inc.  
 DT Journal  
 LA English  
 AB The hybrid was designed and synthesized, which was prepared combining the minor groove binders distamycin A and pyrrolo[2,1-c][1,4]benzodiazepine (PBD) 4, related to the natural occurring anthramycin and DC-81. The effects of the hybrid on mol. interactions between DNA and transcription factor Sp1 were studied. Thus, PBD-distamycin hybrid is a powerful inhibitor of Sp1/DNA interactions.  
 IT 319477-08-2P 319477-11-7P 319477-13-9P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (pyrrolo[2,1-c][1,4]benzodiazepine-distamycin hybrid inhibits DNA binding to transcription factor Sp1)  
 RN 319477-08-2 CAPLUS  
 CN Propanoic acid, 3-[[[(11S,11aS)-10-[3-[(chlorocarbonyl)oxy]-1-propenyl]-2,3,5,10,11,11a-hexahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry unknown.



RN 319477-11-7 CAPLUS  
 CN Propanoic acid, 3-[[[(11S,11aS)-10-[3-[(chlorocarbonyl)oxy]-1-propenyl]-2,3,5,10,11,11a-hexahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]- (9CI) (CA INDEX NAME)

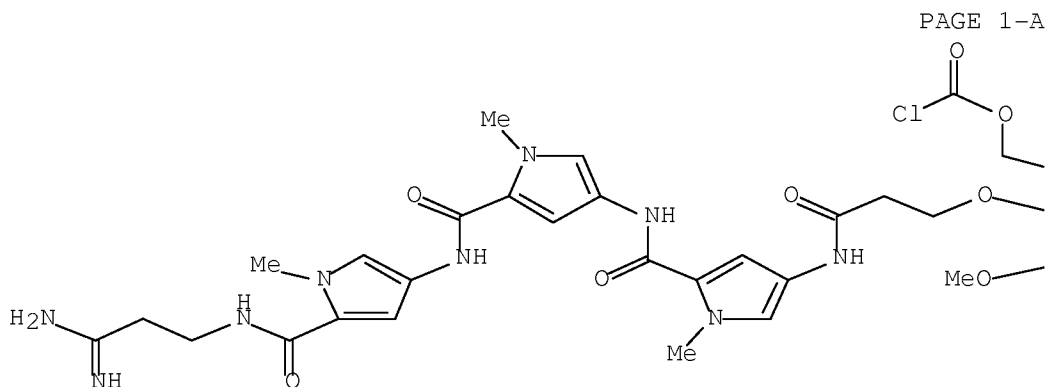
Absolute stereochemistry.  
 Double bond geometry unknown.



RN 319477-13-9 CAPLUS

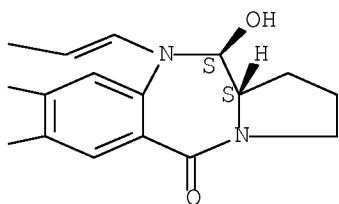
CN Carbonochloridic acid, 3-[(11S,11aS)-8-[3-[5-[5-[5-[5-[(3-amino-3-  
iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-  
methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-3-  
oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-  
pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-yl]-2-propenyl ester,  
monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry unknown.



● HCl

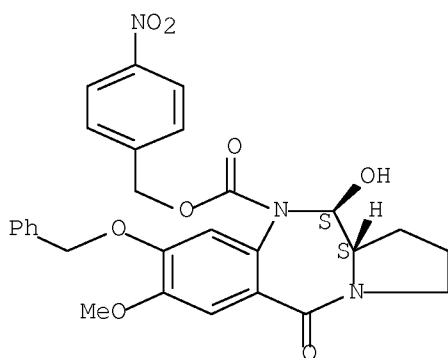




RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

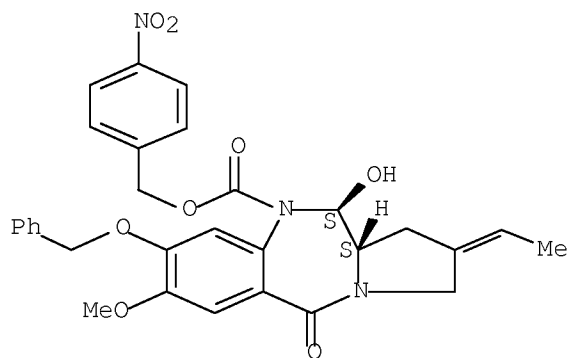
L11 ANSWER 26 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2000:619247 CAPLUS Full-text  
 DN 133:362758  
 TI Design and synthesis of novel pyrrolobenzodiazepine (PBD) prodrugs for ADEPT and GDEPT  
 AU Sagnou, M. J.; Howard, P. W.; Gregson, S. J.; Eno-Amooquaye, E.; Burke, P. J.; Thurston, D. E.  
 CS School of Pharmacy and Biomedical Sciences, CRC Gene Targeting Drug Design Research Group, University of Portsmouth, Hants, PO1 2DT, UK  
 SO Bioorganic & Medicinal Chemistry Letters (2000), 10(18), 2083-2086  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Science Ltd.  
 DT Journal  
 LA English  
 OS CASREACT 133:362758  
 AB Three N10-(4-nitrobenzyl)carbamate-protected PBD prodrugs were prepared and evaluated for potential use in nitro reductase-based ADEPT (antibody-directed enzyme chemotherapy) and GDEPT (gene-directed chemotherapy). For example, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid (4-nitrophenyl)methyl ester was prepared, which is a prodrug precursor to benzyl DC 81. An approx. 100-fold activation was observed for benzyl DC 81.  
 IT 307925-10-6P 307925-11-7P 307925-16-2F  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation of pyrrolobenzodiazepine prodrugs for antibody-directed enzyme chemotherapy (ADEPT) and gene-directed enzyme chemotherapy (GEDEPT))  
 RN 307925-10-6 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-, (4-nitrophenyl)methyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 307925-11-7 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2-ethylidene-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-, (4-nitrophenyl)methyl ester, (11S,11aS)- (CA INDEX NAME)

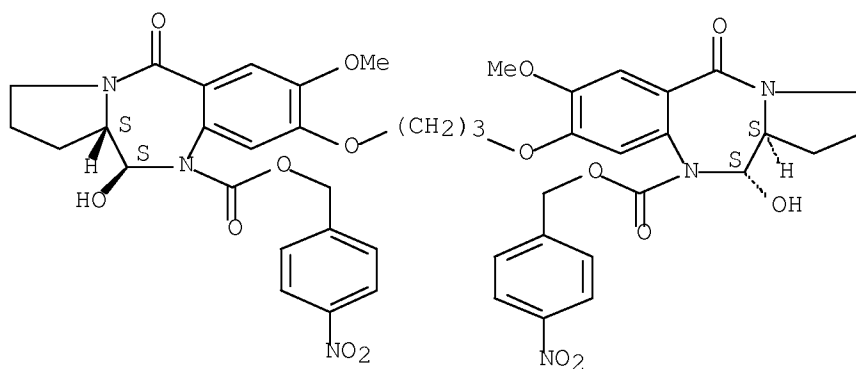
Absolute stereochemistry.  
 Double bond geometry unknown.



RN 307925-16-2 CAPLUS

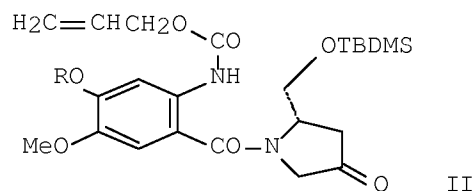
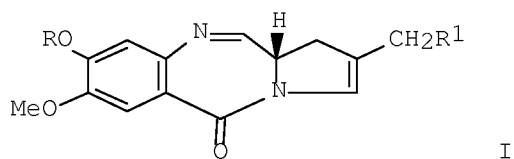
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis[(4-nitrophenyl)methyl] ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



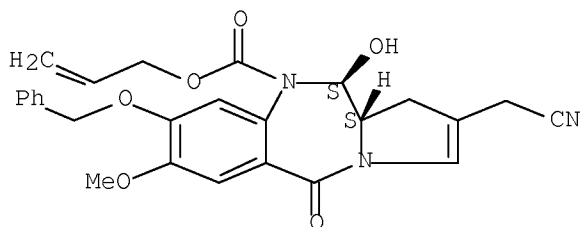
RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 27 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2000:565893 CAPLUS Full-text  
 DN 133:321863  
 TI Effect of C2/C3-endo unsaturation on the cytotoxicity and DNA-binding reactivity of pyrrolo[2,1-c][1,4]benzodiazepines  
 AU Gregson, S. J.; Howard, P. W.; Barcella, S.; Nakamya, A.; Jenkins, T. C.; Kelland, L. R.; Thurston, D. E.  
 CS White Swan Road, St Michael's Building, School of Pharmacy and Biomedical Science, CRC Gene Targeted Drug Design Research Group, University of Portsmouth, Portsmouth, Hants, PO1 2DT, UK  
 SO Bioorganic & Medicinal Chemistry Letters (2000), 10(16), 1849-1851  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Science Ltd.  
 DT Journal  
 LA English  
 GI



AB Pyrrolo[2,1-c][1,4]benzodiazepines I [R = Me, R1 = CO2Me; R = CH2Ph, R1 = CO2Me, CN, CH2OAc, CH2OH] were prepared from the pyrrolidinones II by reaction with (EtO)2P(O)CH2R2 [R2 = CO2Me, CN], desilylation, cyclization and deallyloxycarbonylation with concomitant dehydration. Biophys. and biol. evaluations show that the presence of C2/C3-endo unsatn. in the C-ring enhances both DNA-binding reactivity and in vitro cytotoxic potency.  
 IT 260417-72-9P 260417-79-6P 260417-84-3P  
 260417-85-4P 260417-92-3P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and cytotoxicity and DNA-binding reactivity of pyrrolo[2,1-c][1,4]benzodiazepines)  
 RN 260417-72-9 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2-(cyanomethyl)-11,11a-dihydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-, 2-propenyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

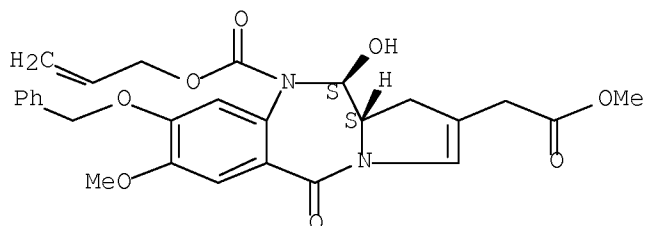
Absolute stereochemistry.



RN 260417-79-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acetic acid, 5,10,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-10-[(2-propenyloxy)carbonyl]-, methyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

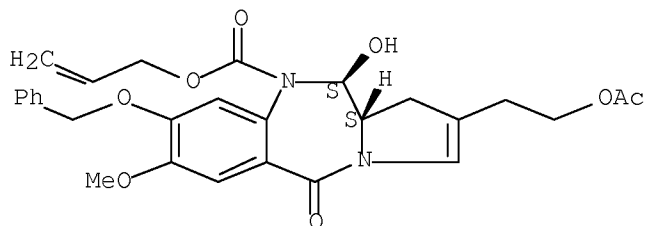
Absolute stereochemistry.



RN 260417-84-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2-[2-(acetyloxy)ethyl]-11,11a-dihydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-, 2-propenyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

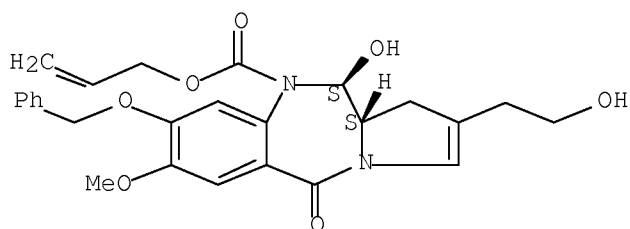
Absolute stereochemistry.



RN 260417-85-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 11,11a-dihydro-11-hydroxy-2-(2-hydroxyethyl)-7-methoxy-5-oxo-8-(phenylmethoxy)-, 2-propenyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

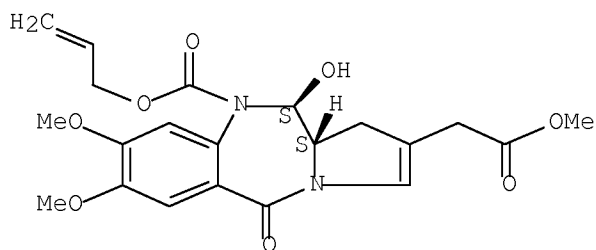
Absolute stereochemistry.



RN 260417-92-3 CAPLUS

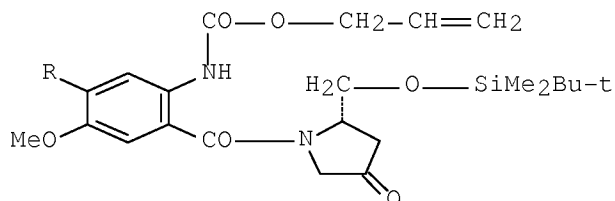
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acetic acid, 5,10,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-10-[(2-propenyloxy)carbonyl]-, methyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

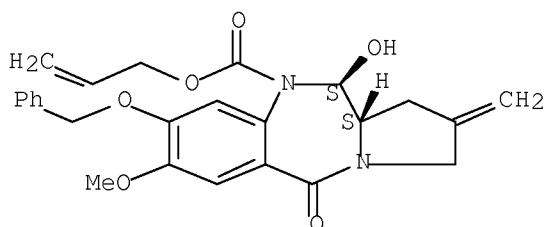
L11 ANSWER 28 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2000:565892 CAPLUS Full-text  
 DN 133:309885  
 TI Effect of C2-exo unsaturation on the cytotoxicity and DNA-binding reactivity of pyrrolo[2,1-c][1,4]benzodiazepines  
 AU Gregson, Stephen J.; Howard, Philip W.; Corcoran, Kathryn E.; Barcella, Simona; Yasin, Maqsood M.; Hurst, Abigail A.; Jenkins, Terence C.; Kelland, Lloyd R.; Thurston, David E.  
 CS School of Pharmacy and Biomedical Science, CRC Gene Targeted Drug Design Research Group, University of Portsmouth, Portsmouth, Hants, PO1 2DT, UK  
 SO Bioorganic & Medicinal Chemistry Letters (2000), 10(16), 1845-1847  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Science Ltd.  
 DT Journal  
 LA English  
 OS CASREACT 133:309885  
 GI



I

AB A series of novel C2-exo unsatd. pyrrolo[2,1-c][1,4]benzodiazepines (PBDs) has been synthesized via a versatile pro-C2 ketone precursor. C2-exo-unsatn. enhances both DNA-binding reactivity and in vitro cytotoxic potency. The ketone intermediates (I; R = MeO, PhCH2O) could be efficiently synthesized on al large scale (> 20 g).  
 IT 260418-19-7P 260418-22-2P 301838-68-6P 301838-70-0P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (effect of C2-exo unsatn. on the cytotoxicity and DNA-binding reactivity of pyrrolobenzodiazepines)  
 RN 260418-19-7 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-8-(phenylmethoxy)-, 2-propenyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

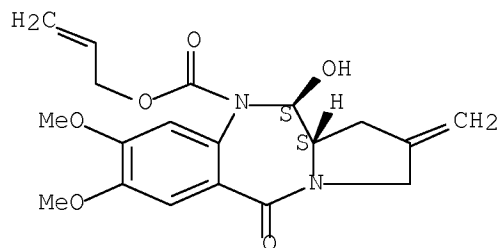
Absolute stereochemistry.



RN 260418-22-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-2-methylene-5-oxo-,  
2-propenyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

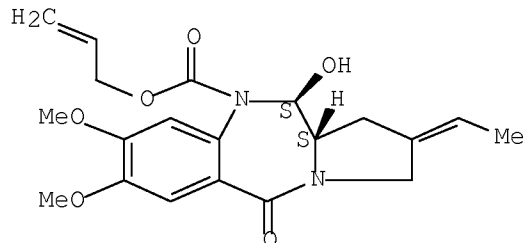
Absolute stereochemistry.



RN 301838-68-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2-ethylidene-2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-,  
2-propenyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

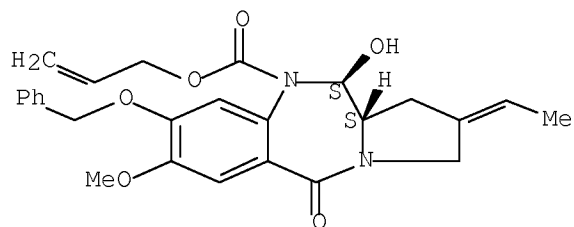
Absolute stereochemistry.  
Double bond geometry unknown.



RN 301838-70-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2-ethylidene-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(  
phenylmethoxy)-, 2-propenyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry unknown.



RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



L11 ANSWER 29 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2000:161285 CAPLUS Full-text  
 DN 132:207852  
 TI Solid-phase preparation and combinatorial libraries of  
 pyrrolobenzodiazepine derivatives for drug screening  
 IN Thurston, David Edwin; Howard, Philip Wilson  
 PA The University of Portsmouth Higher Education Corporation, UK  
 SO PCT Int. Appl., 65 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000012509	A2	20000309	WO 1999-GB2839	19990827
	WO 2000012509	A3	20000706		
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	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2341386	A1	20000309	CA 1999-2341386	19990827
	AU 9955262	A	20000321	AU 1999-55262	19990827
	AU 764464	B2	20030821		
	EP 1107970	A2	20010620	EP 1999-941767	19990827
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002525286	T	20020813	JP 2000-571055	19990827
	NZ 510489	A	20021126	NZ 1999-510489	19990827
	US 6747144	B1	20040608	US 2001-763813	20010226
	US 20040198722	A1	20041007	US 2004-824743	20040415
PRAI	GB 1998-18732	A	19980827		
	WO 1999-GB2839	W	19990827		
	US 2001-763813	A1	20010226		
OS	MARPAT 132:207852				
GI					

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Title compds. I are prepared [wherein: R = (un)substituted alk(en/yn)yl, aralkyl, aryl, or heteroat. analogs; R2 and R3 = H, R, OH, OR, O, :CHR, :CH2, CH2CO2R, CH2CO2H, CH2SO2R, OSO2R, CO2R, COR, and cyano; optionally double bond in ring; R6, R7, R8, and R9 = H, R, OH, OR, halo, NO2, amino, Me3Sn; or R7R8 = O(CH2)1-20; R11 = H or R; Q = S, O, or NH; L = linking group or bond; Sup = solid support; or where 1 or more of R2, R3, R6, R7 and R8 = independently = H-(T)n-X-Y-A- where: X = CO, NH, S or O; T = combinatorial unit; Y = divalent group such that HY = R; A = O, S, NH, or bond; and n = pos. integer]. The compds. are intermediates for pyrrolobenzodiazepine derivs. II, which are claimed as being potentially useful for treatment of bacterial, parasitic, viral, and gene-based diseases. For example, the supported chloroformate ester III underwent (1) elaboration with 4,5-dimethoxyanthranilic acid, (2) amidation with 2-pyrrolidinemethanol, and (3) oxidative cyclization using SO3.pyridine and DMSO, to give the invention compound IV. Photochem. cleavage of IV gave the corresponding amination, which was dehydrated in situ to give the

corresponding compound V. The cleavage product showed cytotoxicity against human leukemia cells which was identical to that of authentic samples of V. Another compound I was derivatized at a sidechain using 3 amino acids in 3 chain positions to give a 27-member combinatorial library.

IT 260417-41-2DP, derivs.

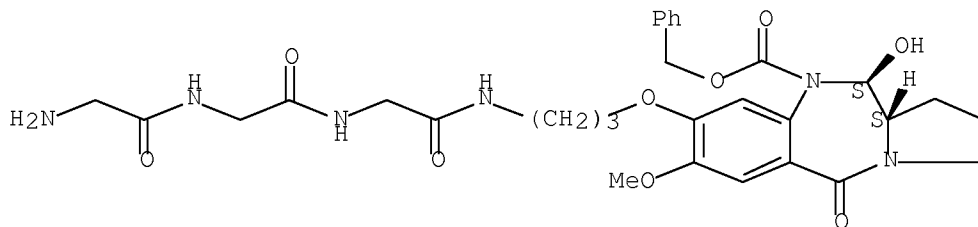
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(combinatorial library; solid-phase preparation and combinatorial libraries of pyrrolobenzodiazepine derivs. for drug screening)

RN 260417-41-2 CAPLUS

CN Glycinamide, glycyglycyl-N-[3-[[[(11R,11aR)-2,3,5,10,11,11a-hexahydro-11-hydroxy-7-methoxy-5-oxo-10-[(phenylmethoxy)carbonyl]-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propyl]- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT 260417-08-1DP, resin-bound 260417-13-8DP, resin-bound

260417-22-9DP, resin-bound 260417-23-0DP, resin-bound

260417-25-2DP, resin-bound 260417-30-9DP, resin-bound

260417-35-4DP, resin-bound 260417-37-6DP, resin-bound

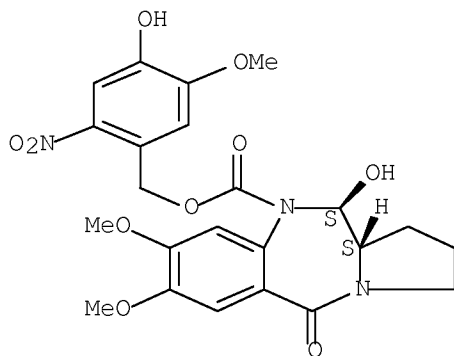
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; solid-phase preparation and combinatorial libraries of pyrrolobenzodiazepine derivs. for drug screening)

RN 260417-08-1 CAPLUS

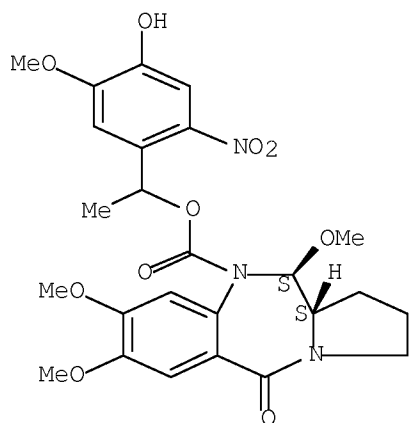
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-, (4-hydroxy-5-methoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (CA INDEX NAME)

Relative stereochemistry.



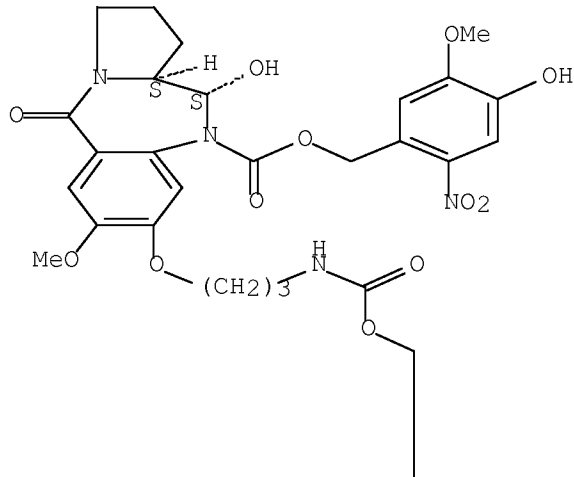
RN 260417-13-8 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-7,8,11-trimethoxy-5-oxo-, 1-(4-hydroxy-5-methoxy-2-nitrophenyl)ethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

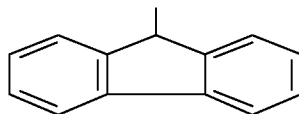


RN 260417-22-9 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-[3-[[[9H-fluoren-9-ylmethoxy)carbonyl]amino]propoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, (4-hydroxy-5-methoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (CA INDEX NAME)

Relative stereochemistry.



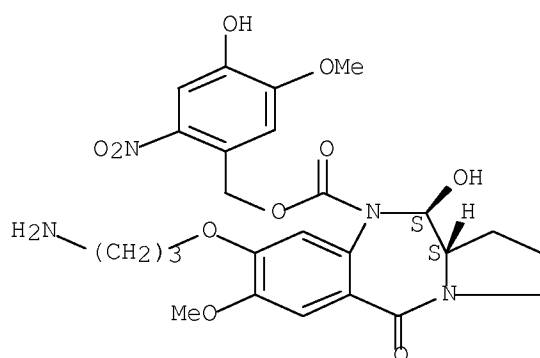
PAGE 1-A



RN 260417-23-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(3-aminopropoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
(4-hydroxy-5-methoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (CA  
INDEX NAME)

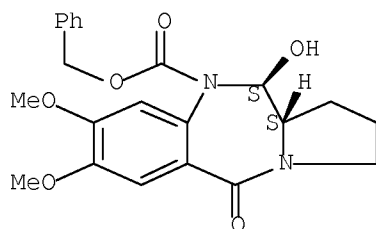
Relative stereochemistry.



RN 260417-25-2 CAPLUS

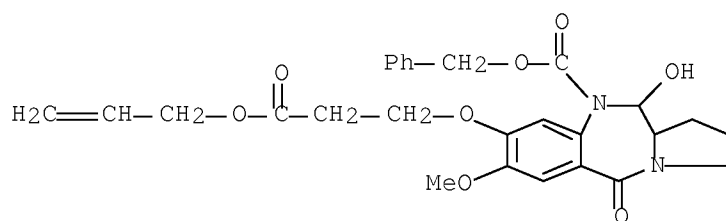
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-, phenylmethyl ester,  
(11R,11aR)-rel- (CA INDEX NAME)

Relative stereochemistry.



RN 260417-30-9 CAPLUS

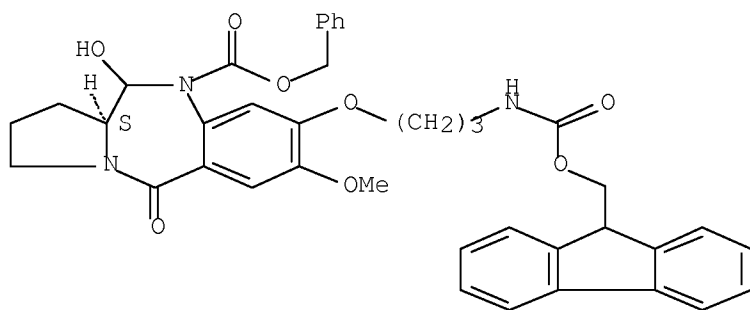
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-  
propenyloxy)propoxy]-, phenylmethyl ester (9CI) (CA INDEX NAME)



RN 260417-35-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[3-[[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]propoxy]-2,3,11,11a-  
tetrahydro-11-hydroxy-7-methoxy-5-oxo-, phenylmethyl ester, (11aS)- (CA  
INDEX NAME)

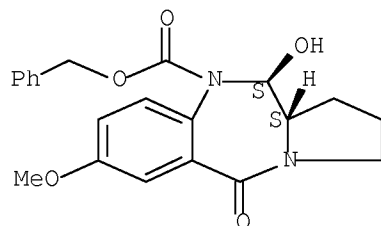
Absolute stereochemistry.



RN 260417-37-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, phenylmethyl ester,  
(11R,11aR)-rel- (CA INDEX NAME)

Relative stereochemistry.



L11 ANSWER 30 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2000:161284 CAPLUS Full-text

DN 132:207851

TI Preparation of pyrrolobenzodiazepines (PBDs) as antitumor agents

IN Thurston, David Edwin; Howard, Philip Wilson

PA The University of Portsmouth Higher Education Corporation, UK

SO PCT Int. Appl., 258 pp.

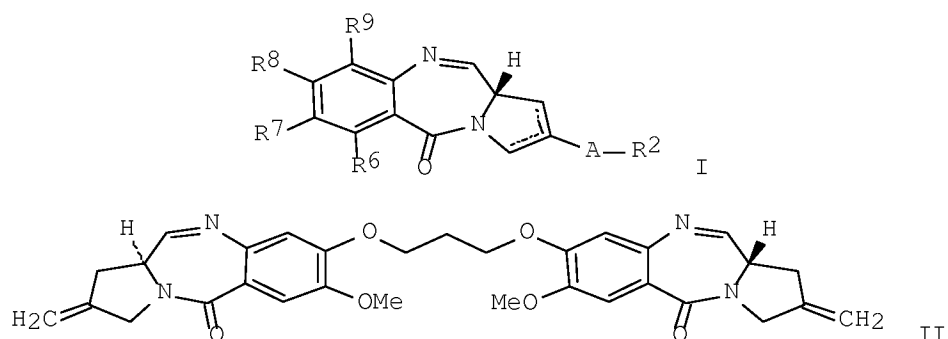
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 2000012508	A2	20000309	WO 1999-GB2838	19990827
	WO 2000012508	A3	20000921		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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	AU 9956351	A	20000321	AU 1999-56351	19990827
	AU 757510	B2	20030220		
	EP 1109812	A2	20010627	EP 1999-943066	19990827
	EP 1109812	B1	20050504		
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	EP 1193270	A2	20020403	EP 2001-129700	19990827
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	EP 1193270	B1	20030514		
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	JP 2002525285	T	20020813	JP 2000-571054	19990827
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	PT 1193270	T	20031031	PT 2001-129700	19990827
	NZ 510493	A	20031128	NZ 1999-510493	19990827
	ES 2199200	T3	20040216	ES 2001-129700	19990827
	EP 1413582	A1	20040428	EP 2003-28817	19990827
	EP 1413582	B1	20060315		
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	AT 320436	T	20060415	AT 2003-28817	19990827
	PT 1413582	T	20060731	PT 2003-28817	19990827
	ES 2260570	T3	20061101	ES 2003-28817	19990827
	US 7049311	B1	20060523	US 2001-763767	20010226
	US 20030120069	A1	20030626	US 2001-21213	20011212
	US 7067511	B2	20060627		
	US 20060148788	A1	20060706	US 2006-367241	20060302
	US 7265105	B2	20070904		
PRAI	GB 1998-18733	A	19980827		
	GB 1999-1929	A	19990128		
	EP 1999-943066	A3	19990827		
	WO 1999-GB2838	W	19990827		
	US 2001-763767	A1	20010226		



AB 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one derivs. (I) [wherein A = CH<sub>2</sub> or a single bond; R = (un)substituted (ar)alkyl, (ar)alkenyl, or (ar)alkynyl; R<sub>2</sub> = R, OH, OR, CO<sub>2</sub>H, CO<sub>2</sub>R, COH, COR, SO<sub>2</sub>R, CN; R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, and R<sub>9</sub> = independently H, R, OH, OR, halo, NH<sub>2</sub>, NHR, NO<sub>2</sub>, SnMe<sub>3</sub>; or the compound is a dimer with each monomer being the same or different and being of formula I and the R<sub>8</sub> groups of the monomers form a -X-R'-X- bridge, where R' is an alkylene chain which may contain ≥ 1 heteroatoms and/or aromatic rings and/or carbon-carbon double or triple bonds, and each X = independently O, S, or N] were prepared for the treatment of gene-based diseases, e.g. neoplastic diseases and Alzheimer's disease, and also bacterial, parasitic, and viral infections. For example, II was synthesized in a 6-step sequence. 1',3'-Bis(4-carboxy-2-methoxy-5-nitrophenoxy)propane (preparation given) was bisamidated with (2S)-2-(tert-butylidimethylsilyloxymethyl)-4-methylenepyrrolidine (74%). TBAF-mediated cleavage of the silyl protecting groups (94%), followed by reduction of the nitro groups by NH<sub>2</sub>NH<sub>2</sub> in the presence of Raney Ni (63%) and N-acylation with allyl chloroformate (50%), gave the protected diamine. Ring closure was accomplished under Swern oxidation conditions, (COCl)<sub>2</sub>-DMSO and TEA, (32%). Finally, the imine was formed from the carbinolamine by N-deprotection using Pd(PPh<sub>3</sub>)<sub>4</sub> and elimination of H<sub>2</sub>O (77%). Both large scale in vitro cytotoxicity cell screens and in vivo hollow fiber and human tumor xenograft assays were performed on selected compds. of the invention. For instance, II exhibited potent and selective cytotoxicity against the lung cancer cell line NCI-H460, the colon cell line HCC-2998, the CNS cancer cell line SNB-75, and the melanoma cell lines MALME-3M (very potent, 0.08 μM) and UACC-62 (very potent, 0.07 μM). In human xenograft studies against five types of tumors, II demonstrated anticancer activity with mixed toxicity results. In addition, II was shown to be the most potent DNA-stabilizing agent known to date according to a DNA helix melting temperature assay. The IC<sub>50</sub> value for II in the A2780 human ovarian carcinoma cell line was only 23 pM, a 320-fold increase in cytotoxicity compared to the known antitumor agent DSB-120 (IC<sub>50</sub> = 5.2 nM). Remarkably, II was also almost 9000-fold more potent in the cisplatin-resistant A2780cisR cell line (IC<sub>50</sub> = 24 pM) than DSB-120 (IC<sub>50</sub> = 0.21 mM), suggesting that II may have potential in the treatment of cisplatin-refractory disease.

II 232931-64-5P 260417-72-9P 260417-79-6P  
260417-84-3P 260417-85-4P 260417-92-3P  
260418-01-7P 260418-19-7P 260418-22-2P

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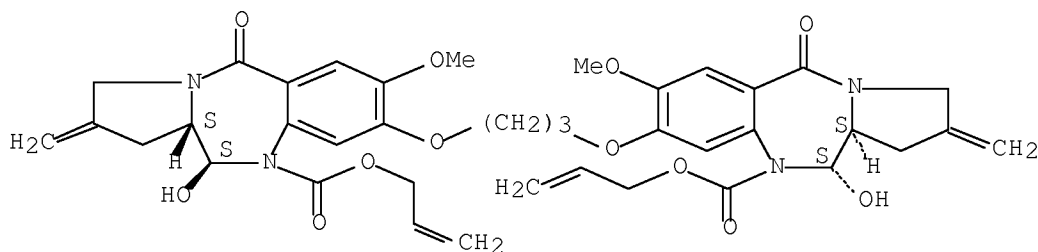
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of 5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one antitumor agents from 2-amino- or 2-nitrobenzoic acid derivs. and pyrrolidines)

RN 232931-64-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

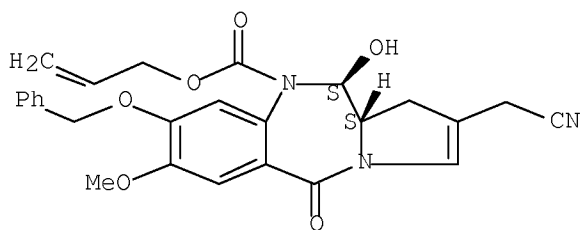
Absolute stereochemistry.



RN 260417-72-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2-(cyanomethyl)-11,11a-dihydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-, 2-propenyl ester, (11S,11aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

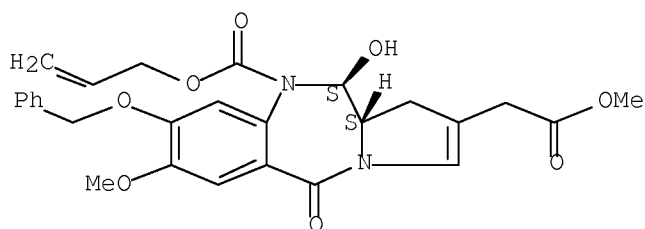


RN 260417-79-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acetic acid, 5,10,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-10-[(2-propenyloxy)carbonyl]-, methyl ester, (11S,11aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

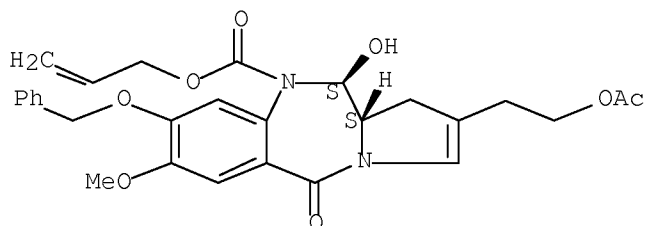




RN 260417-84-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2-[2-(acetyloxy)ethyl]-11,11a-dihydro-11-hydroxy-7-methoxy-5-oxo-8-  
(phenylmethoxy)-, 2-propenyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

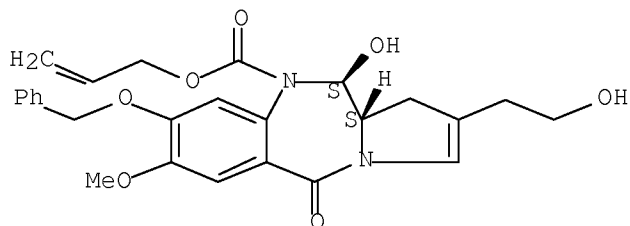
Absolute stereochemistry.



RN 260417-85-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
11,11a-dihydro-11-hydroxy-2-(2-hydroxyethyl)-7-methoxy-5-oxo-8-  
(phenylmethoxy)-, 2-propenyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

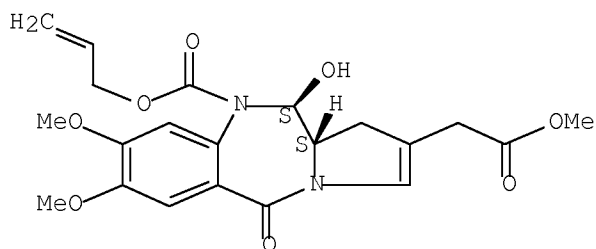
Absolute stereochemistry.



RN 260417-92-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acetic acid, 5,10,11,11a-tetrahydro-  
11-hydroxy-7,8-dimethoxy-5-oxo-10-[(2-propenyloxy)carbonyl]-, methyl  
ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

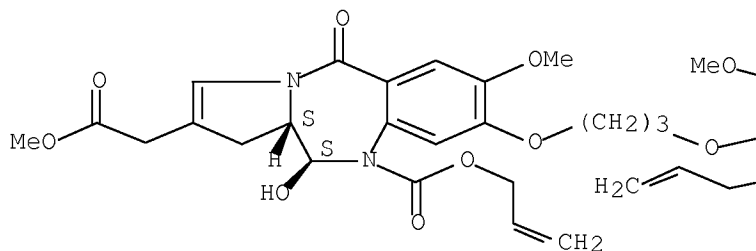


RN 260418-01-7 CAPLUS

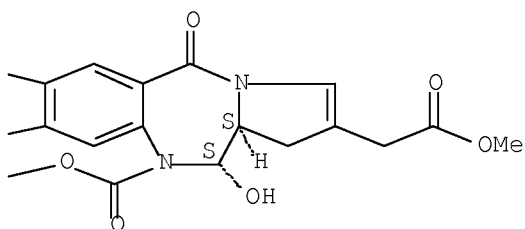
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acetic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[5,10,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-10-[(2-propenyloxy)carbonyl]-, dimethyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



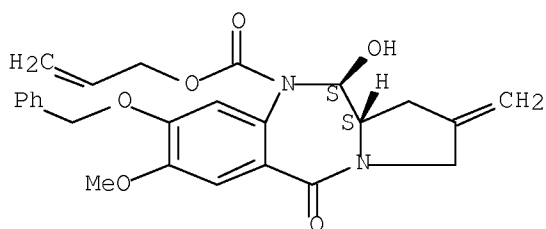
PAGE 1-B



RN 260418-19-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-8-(phenylmethoxy)-, 2-propenyl ester, (11S,11aS)-(9CI) (CA INDEX NAME)

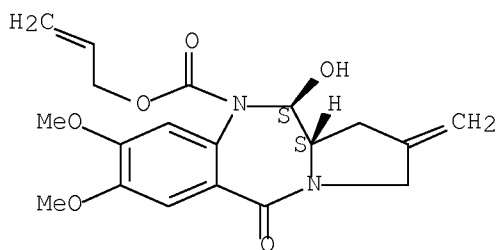
Absolute stereochemistry.



RN 260418-22-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-2-methylene-5-oxo-,  
2-propenyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

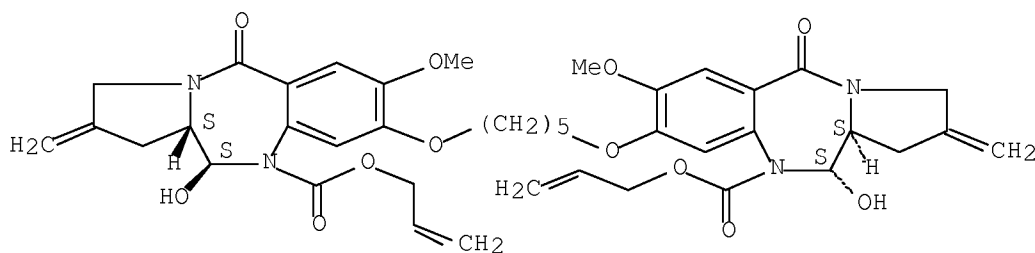
Absolute stereochemistry.



RN 260418-31-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,5-pentandiylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-  
(9CI) (CA INDEX NAME)

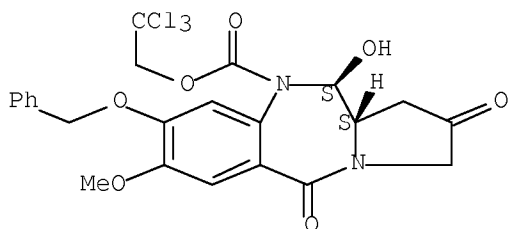
Absolute stereochemistry.



RN 260418-35-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2,5-dioxo-8-(phenylmethoxy)-,  
2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

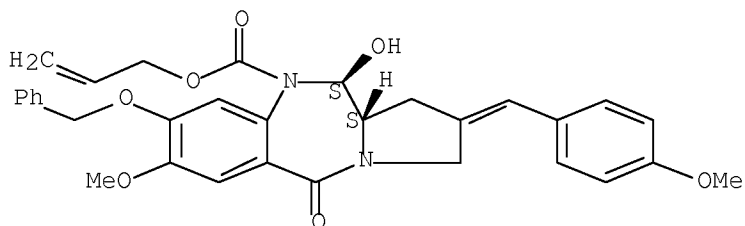
Absolute stereochemistry.



RN 260418-38-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-[(4-methoxyphenyl)methylene]-5-oxo-8-(phenylmethoxy)-, 2-propenyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

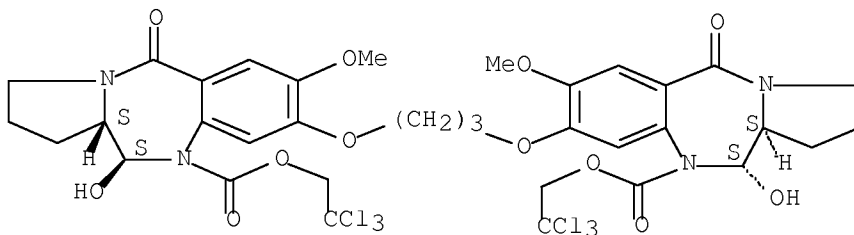
Absolute stereochemistry.  
Double bond geometry unknown.



RN 260418-44-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

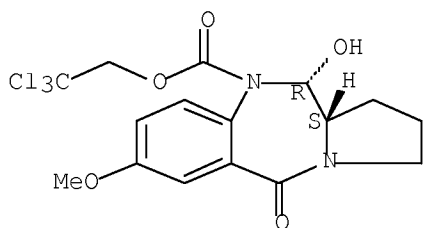
Absolute stereochemistry.



RN 260418-47-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, (11R,11aS)- (CA INDEX NAME)

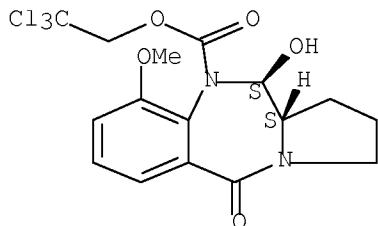
Absolute stereochemistry.



RN 260418-50-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-9-methoxy-5-oxo-, 2,2,2-trichloroethyl  
ester, (11S,11aS)- (CA INDEX NAME)

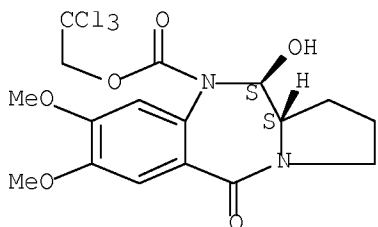
Absolute stereochemistry.



RN 260418-53-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-,  
2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

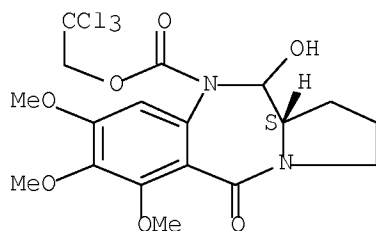
Absolute stereochemistry. Rotation (+).



RN 260418-57-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-6,7,8-trimethoxy-5-oxo-,  
2,2,2-trichloroethyl ester, (11aS)- (CA INDEX NAME)

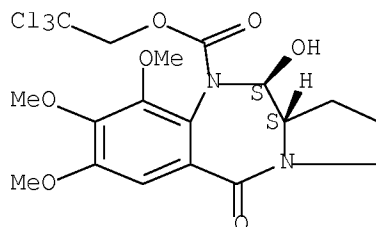
Absolute stereochemistry.



RN 260418-60-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7,8,9-trimethoxy-5-oxo-,  
2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

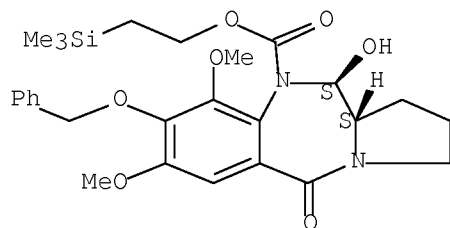
Absolute stereochemistry.



RN 260419-01-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7,9-dimethoxy-5-oxo-8-(phenylmethoxy)-,  
2-(trimethylsilyl)ethyl ester, (11S,11aS)- (CA INDEX NAME)

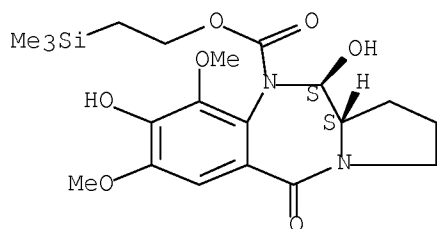
Absolute stereochemistry.



RN 260419-07-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-8,11-dihydroxy-7,9-dimethoxy-5-oxo-,  
2-(trimethylsilyl)ethyl ester, (11S,11aS)- (CA INDEX NAME)

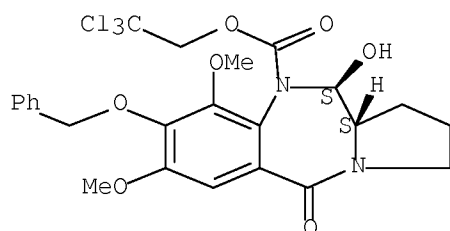
Absolute stereochemistry.



RN 260419-46-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7,9-dimethoxy-5-oxo-8-(phenylmethoxy)-,  
2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

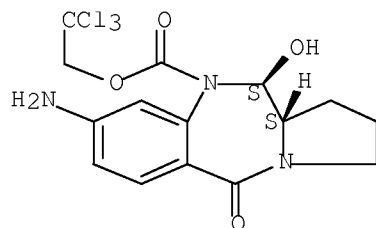
Absolute stereochemistry.



RN 260419-71-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-amino-2,3,11,11a-tetrahydro-11-hydroxy-5-oxo-, 2,2,2-trichloroethyl  
ester, (11S,11aS)- (CA INDEX NAME)

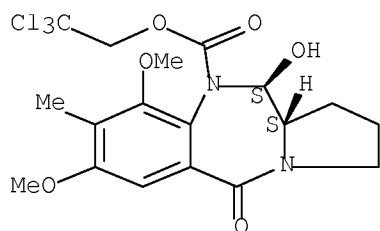
Absolute stereochemistry.



RN 260420-13-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7,9-dimethoxy-8-methyl-5-oxo-,  
2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

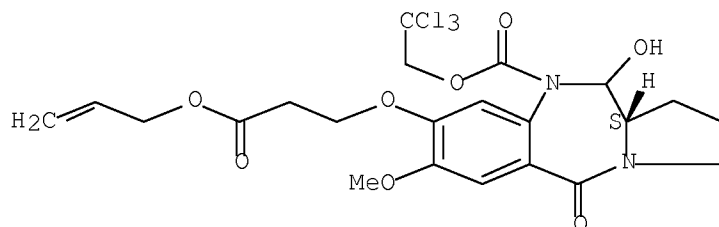
Absolute stereochemistry.



RN 260420-49-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-propenyloxy)propoxy]-, 2,2,2-trichloroethyl ester, (11aS)- (9CI) (CA INDEX NAME)

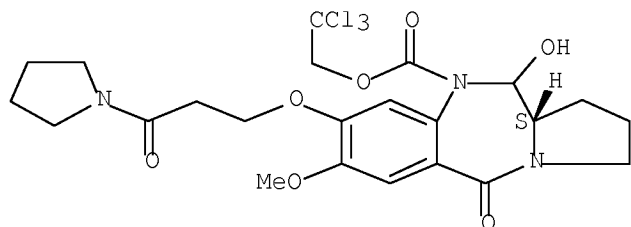
Absolute stereochemistry.



RN 260420-55-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(1-pyrrolidinyl)propoxy]-, 2,2,2-trichloroethyl ester, (11aS)- (CA INDEX NAME)

Absolute stereochemistry.

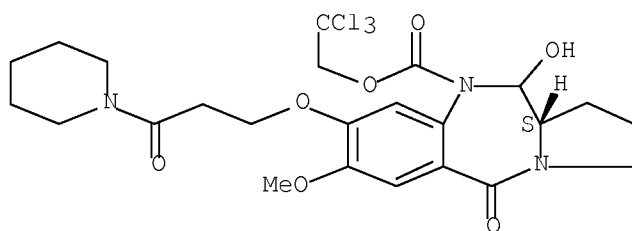


RN 260420-61-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(1-piperidinyl)propoxy]-, 2,2,2-trichloroethyl ester, (11aS)- (CA INDEX NAME)



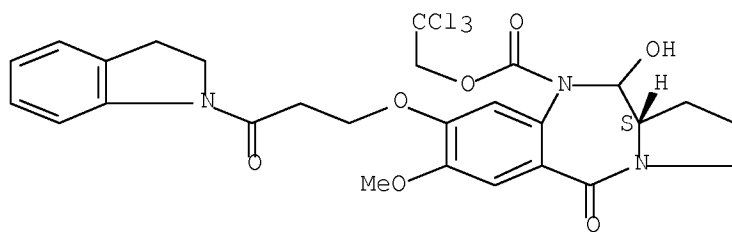
Absolute stereochemistry.



RN 260420-67-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[3-(2,3-dihydro-1H-indol-1-yl)-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-  
hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, (11aS)- (CA INDEX  
NAME)

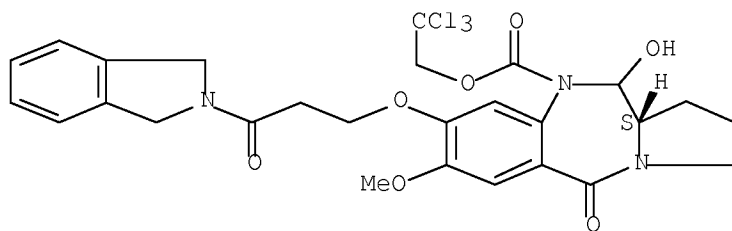
Absolute stereochemistry.



RN 260420-74-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[3-(1,3-dihydro-2H-isoindol-2-yl)-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-  
hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, (11aS)- (CA INDEX  
NAME)

Absolute stereochemistry.

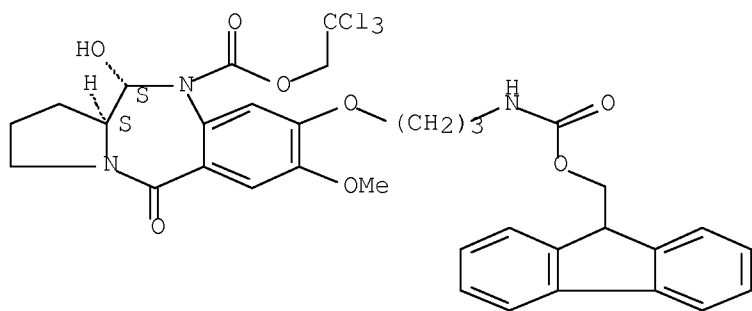


RN 260421-18-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[3-[[ (9H-fluoren-9-ylmethoxy) carbonyl] amino]propoxy]-2,3,11,11a-  
tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester,

(11S,11aS)- (CA INDEX NAME)

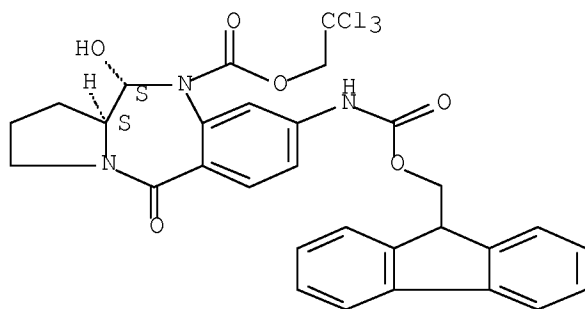
Absolute stereochemistry.



RN 260422-13-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-2,3,11,11a-tetrahydro-11-  
hydroxy-5-oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



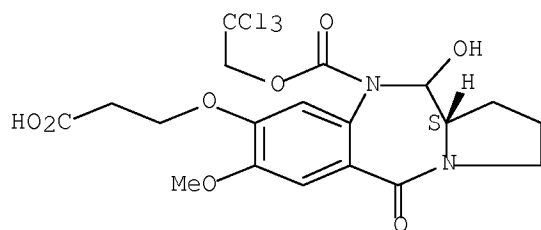
IT 260417-65-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(target compound; preparation of 5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one antitumor agents from 2-amino- or 2-nitrobenzoic acid derivs. and pyrrolidines)

RN 260417-65-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
10-(2,2,2-trichloroethyl) ester, (11aS)- (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 31 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2000:161283 CAPLUS Full-text

DN 132:207703

TI Preparation of pyrrolobenzodiazepines (PBDs) as antitumor antibiotics

IN Thurston, David Edwin; Howard, Philip Wilson

PA The University of Portsmouth Higher Education Corporation, UK

SO PCT Int. Appl., 101 pp.

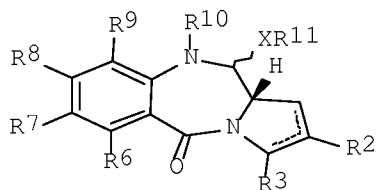
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DT Patent

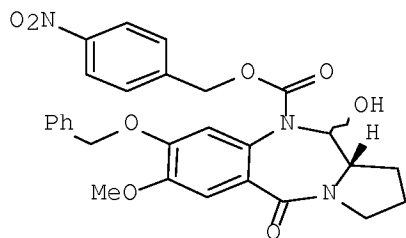
LA English

FAN.CNT 1

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	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
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GI					



I



II

AB 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one derivs. (I) [wherein R = (un)substituted (ar)alkyl, etc.; R2 and R3 = independently H, R, OH, OR, =O, =CH-R, =CH2, CH2-CO2R, CH2-CO2H, CH2-SO2R, O-SO2-R, CO2R, COR, or CN; R6, R7, R8, and R9 = independently H, R, OH, OR, halo, NH2, NO2, or Me3Sn; or R7 and R8 together form a -O-(CH2)p-O- group, where p = 1 or 2; or the compound is a dimer with each monomer being the same or different and being of formula I and the R8 groups of the monomers form a -T-R'-T- bridge, where R' is an alkylene chain which may contain  $\geq 1$  heteroatoms and/or aromatic rings and/or carbon-carbon double or triple bonds, and each T = independently O, S, or N; R10 = a therapeutically removable N-protecting group; R11 = H or R; X is S, O, or NH] were prepared for the treatment of cancer and other site-specific diseases where a local increase of toxicity is beneficial to the patient. Examples include the syntheses of benzyl DC-81, benzyl tomaymycin, and DSB-120 prodrugs starting from 2-nitrobenzoic acid derivs. and pyrrolidines. Data from enzyme and light activation studies and cytotoxicity assays are also given. For example, the nitroreductase-activated benzyl DC-81 (II) was formed in a 6-step sequence involving: (1) benzylation of vanillic acid (67%); (2) ring nitration (82%); (3) amidation with (2S)-pyrrolidinemethanol (88%); (4) reduction of the nitro group (81%); (5) N-addition of 4-nitrobenzyl chloroformate; and (6) cyclization using Swern oxidation conditions (31%). In the presence of nitroreductase and the NADH co-factor, II demonstrated antitumor activity (IC50 = 1-5  $\mu$ M) against the SW1116 and LS174T human adenocarcinoma colonic cell lines. II proved non-toxic in SW1116 cells at concns.  $\leq$  500  $\mu$ M and showed slight toxicity in LS174T cells at concns.  $>$  100  $\mu$ M. I may also be suitable for treating bacterial, parasitic, or viral infections by exploiting a unique enzyme produced at the site of infection which is not natural to the host, or by exploiting an elevation in the amount of an enzyme which does occur naturally in the host.

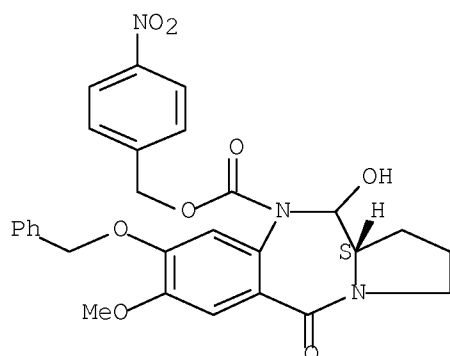
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 260391-42-2P 260391-43-3P 260391-44-4P  
 260391-45-5P 260391-46-6P 260391-47-7P  
 260391-48-8P

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (target compound; preparation of pyrrolobenzodiazepinone prodrugs from 2-nitrobenzoic acid derivs. and pyrrolidines for the treatment of cancer)

RN 260391-39-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-, (4-nitrophenyl)methyl ester, (11aS)- (CA INDEX NAME)

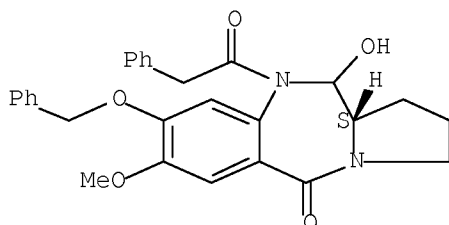
Absolute stereochemistry.



RN 260391-40-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-11-hydroxy-7-methoxy-10-(phenylacetyl)-8-(phenylmethoxy)-, (11aS)- (9CI) (CA INDEX NAME)

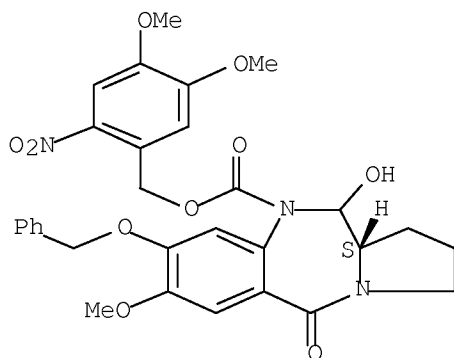
Absolute stereochemistry.



RN 260391-41-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-, (4,5-dimethoxy-2-nitrophenyl)methyl ester, (11aS)- (CA INDEX NAME)

Absolute stereochemistry.

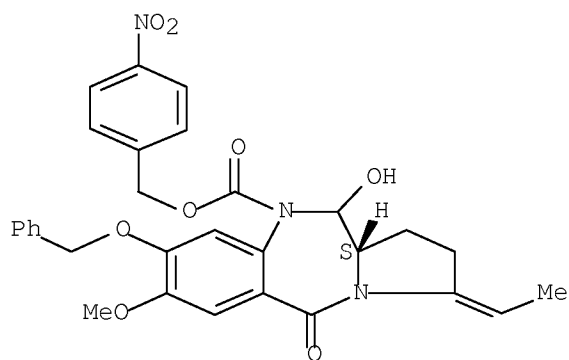


RN 260391-42-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 3-ethylidene-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-, (4-nitrophenyl)methyl ester, (11aS)- (CA INDEX NAME)

Absolute stereochemistry.

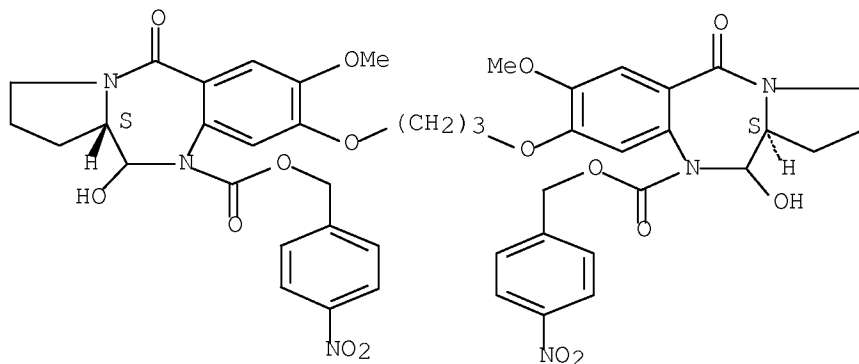
Double bond geometry unknown.



RN 260391-43-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
methoxy-5-oxo-, bis[(4-nitrophenyl)methyl] ester, (11aS,11'aS)- (9CI) (CA  
INDEX NAME)

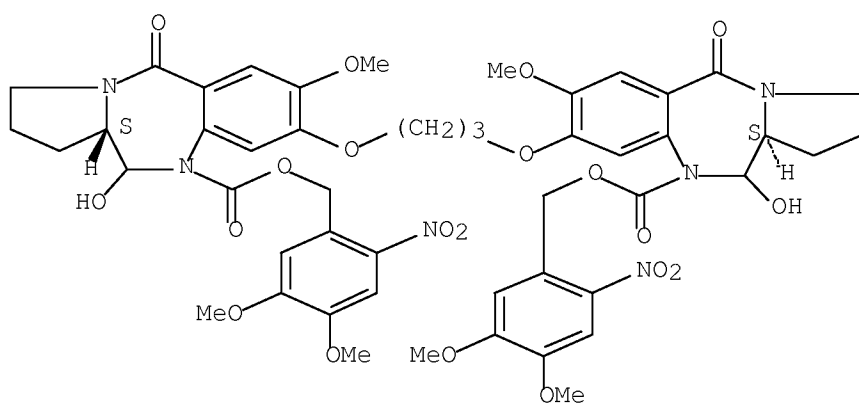
Absolute stereochemistry.



RN 260391-44-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
methoxy-5-oxo-, bis[(4,5-dimethoxy-2-nitrophenyl)methyl] ester,  
(11aS,11'aS)- (9CI) (CA INDEX NAME)

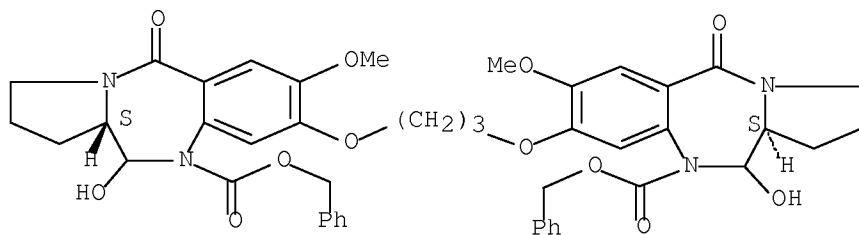
Absolute stereochemistry.



RN 260391-45-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
methoxy-5-oxo-, bis(phenylmethyl) ester, (11aS,11'aS)- (9CI) (CA INDEX  
NAME)

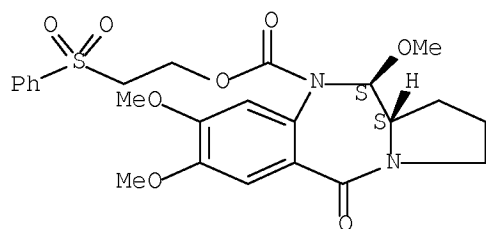
Absolute stereochemistry.



RN 260391-46-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7,8,11-trimethoxy-5-oxo-, 2-(phenylsulfonyl)ethyl  
ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

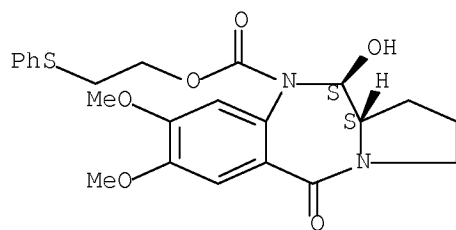


RN 260391-47-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,

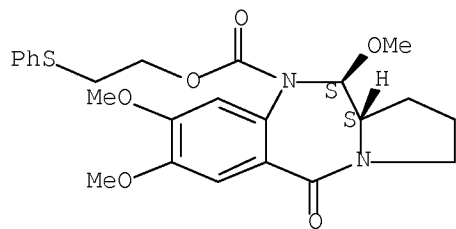
2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-, 2-(phenylthio)ethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



RN 260391-48-8 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-7,8,11-trimethoxy-5-oxo-, 2-(phenylthio)ethyl ester,  
(11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.





L11 ANSWER 32 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2000:161282 CAPLUS Full-text

DN 132:208134

TI Preparation of peptidyl pyrrollobenzodiazepines as pharmaceuticals

IN Thurston, David Edwin; Howard, Philip Wilson

PA The University of Portsmouth Higher Education Corporation, UK

SO PCT Int. Appl., 158 pp.

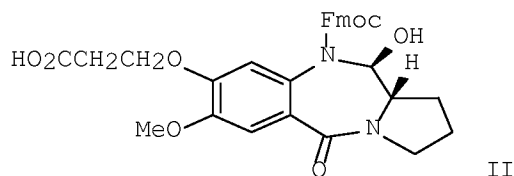
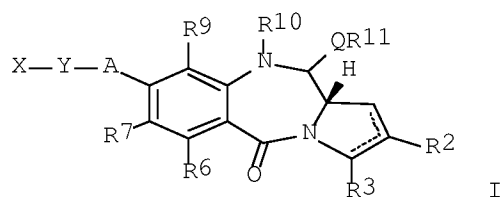
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 2000012506	A2	20000309	WO 1999-GB2836	19990827
	WO 2000012506	A3	20000629		
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	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2341434	A1	20000309	CA 1999-2341434	19990827
	AU 9955260	A	20000321	AU 1999-55260	19990827
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	EP 1107969	A2	20010620	EP 1999-941765	19990827
	EP 1107969	B1	20080116		
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	JP 2002525283	T	20020813	JP 2000-571052	19990827
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	US 6608192	B1	20030819	US 2001-763768	20010226
	US 20040092736	A1	20040513	US 2003-602521	20030624
PRAI	GB 1998-18730	A	19980827		
	WO 1999-GB2836	W	19990827		
	US 2001-763768	A1	20010226		
OS	MARPAT 132:208134				
GI					



AB Benzodiazepines I [X = CO<sub>2</sub>H, NH<sub>2</sub> or protected amino, SH, OH; A = O, S, NH, or a single bond; R<sub>2</sub>, R<sub>3</sub> = H, R, OH, OR, :O, :CHR, :CH<sub>2</sub>, CH<sub>2</sub>CO<sub>2</sub>R, CH<sub>2</sub>CO<sub>2</sub>H, CH<sub>2</sub>SO<sub>2</sub>R, OSO<sub>2</sub>R, CO<sub>2</sub>R, COR, CN, where R = alkyl, alkenyl, alkynyl, aralkyl, (un)substituted aryl; there is optionally a double bond between C<sub>1</sub> and C<sub>2</sub> or C<sub>2</sub> and C<sub>3</sub>; R<sub>6</sub>, R<sub>7</sub>, R<sub>9</sub> = H, R, OH, OR, halo, nitro, amino, Me<sub>3</sub>Sn; R<sub>11</sub> = H or R; Q = S, O or NH; R<sub>10</sub> is a nitrogen-protecting group; Y is a divalent group such that HY = R] were prepared and incorporated into peptides for use as pharmaceuticals. Thus, pyrrolo[2,1- c][1,4]benzodiazepine derivative II (Fmoc = fluorenylmethoxycarbonyl) was prepared and applied to the synthesis of a 27-member glycine/valine/phenylalanine tripeptide library which was screened for inhibition of leukemia cells.

IT 256949-59-4P 260449-57-8P 260449-60-3P  
260449-61-4P 260449-63-6P 260449-64-7P  
260449-66-9P 260449-67-0P 260450-78-0P

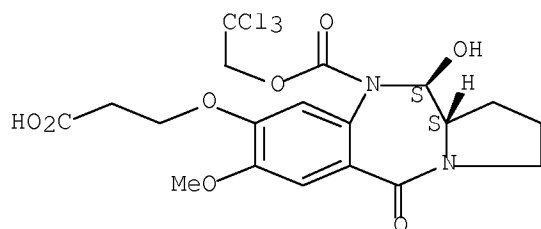
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of peptidyl pyrrolobenzodiazepines as pharmaceuticals)

RN 256949-59-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
10-(2,2,2-trichloroethyl) ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

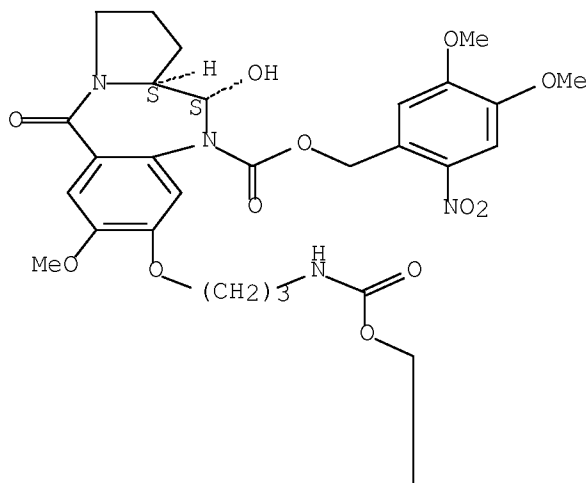


RN 260449-57-8 CAPLUS

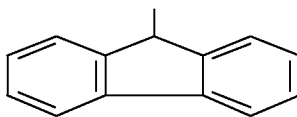
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[3-[[ (9H-fluoren-9-ylmethoxy)carbonyl]amino]propoxy]-2,3,11,11a-  
tetrahydro-11-hydroxy-7-methoxy-5-oxo-, (4,5-dimethoxy-2-  
nitrophenyl)methyl ester, (11R,11aR)-rel- (CA INDEX NAME)

Relative stereochemistry.

PAGE 1-A



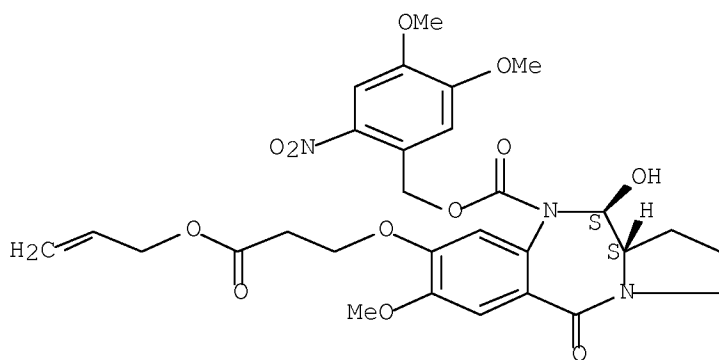
PAGE 2-A



RN 260449-60-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-  
propenyloxy)propoxy]-, (4,5-dimethoxy-2-nitrophenyl)methyl ester,  
(11R,11aR)-rel- (9CI) (CA INDEX NAME)

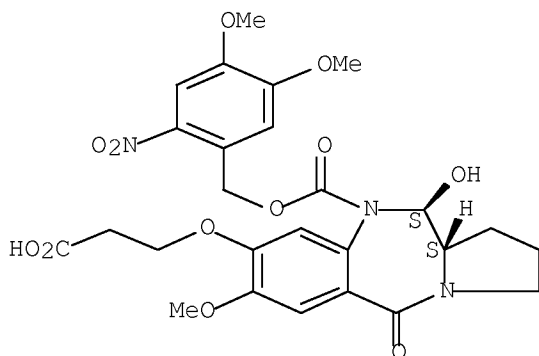
Relative stereochemistry.



RN 260449-61-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
10-[(4,5-dimethoxy-2-nitrophenyl)methyl] ester, (11R,11aR)-rel- (CA INDEX  
NAME)

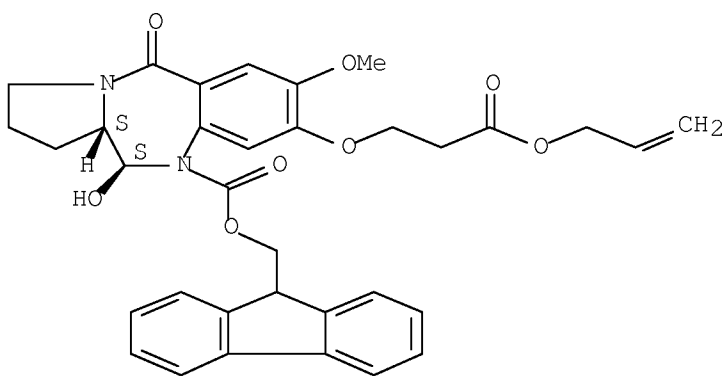
Relative stereochemistry.



RN 260449-63-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-  
propenyloxy)propoxy]-, 9H-fluoren-9-ylmethyl ester, (11R,11aR)-rel- (9CI)  
(CA INDEX NAME)

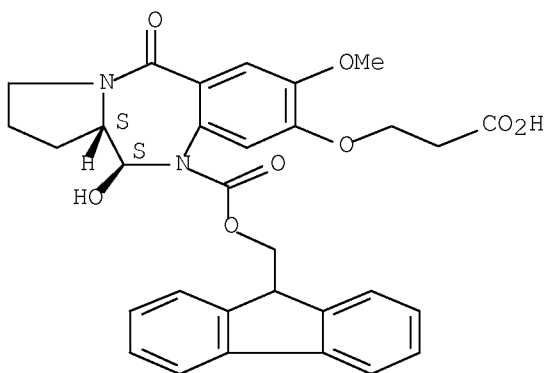
Relative stereochemistry.



RN 260449-64-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
10-(9H-fluoren-9-ylmethyl) ester, (11R,11aR)-rel- (CA INDEX NAME)

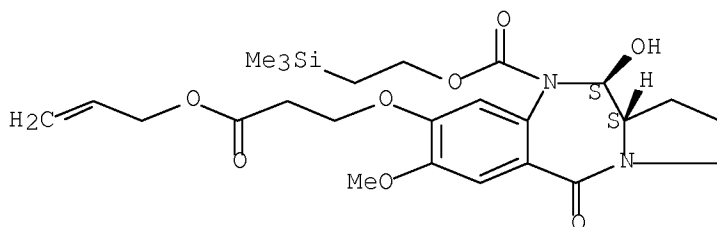
Relative stereochemistry.



RN 260449-66-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-  
propenyloxy)propoxy]-, 2-(trimethylsilyl)ethyl ester, (11R,11aR)-rel-  
(9CI) (CA INDEX NAME)

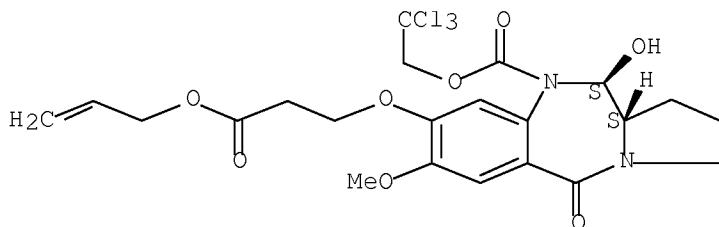
Relative stereochemistry.



RN 260449-67-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-  
propenyloxy)propoxy]-, 2,2,2-trichloroethyl ester, (11S,11aS)- (9CI) (CA  
INDEX NAME)

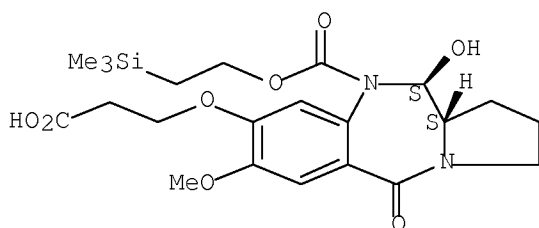
Absolute stereochemistry.



RN 260450-78-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
10-[2-(trimethylsilyl)ethyl] ester, (11R,11aR)-rel- (CA INDEX NAME)

Relative stereochemistry.



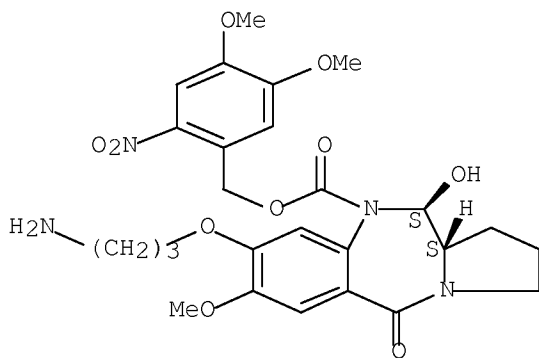
IT 260449-58-9P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of peptidyl pyrrolobenzodiazepines as pharmaceuticals)

RN 260449-58-9 CAPLUS

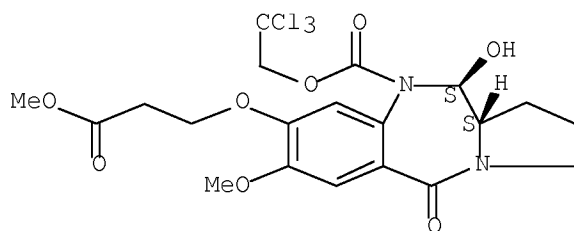
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-(3-aminopropoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
(4,5-dimethoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (CA INDEX  
NAME)

Relative stereochemistry.



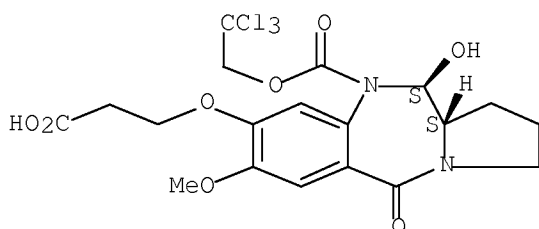
L11 ANSWER 33 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1999:758546 CAPLUS Full-text  
 DN 132:137361  
 TI Synthesis, in Vitro Antiproliferative Activity, and DNA-Binding Properties  
 of Hybrid Molecules Containing Pyrrolo[2,1-c][1,4]benzodiazepine and  
 Minor-Groove-Binding Oligopyrrole Carriers  
 AU Baraldi, Pier Giovanni; Balboni, Gianfranco; Cacciari, Barbara; Guiotto,  
 Andrea; Manfredini, Stefano; Romagnoli, Romeo; Spalluto, Giampiero;  
 Thurston, David E.; Howard, Philip W.; Bianchi, Nicoletta; Rutigliano,  
 Cristina; Mischiati, Carlo; Gambari, Roberto  
 CS Dipartimento di Scienze Farmaceutiche e Dipartimento di Biochimica e  
 Biologia Molecolare, Universita di Ferrara, Ferrara, 44100, Italy  
 SO Journal of Medicinal Chemistry (1999), 42(25), 5131-5141  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 132:137361  
 AB The synthesis, biol. activity, and DNA-binding properties of a series of four  
 pyrrolo[2,1-c][1,4]benzodiazepine (PBD) hybrids containing polypyrrole side  
 chains are described and structure-activity relationships examined To  
 investigate sequence selectivity and stability of drug/DNA complexes, DNase I  
 footprinting and arrested polymerase chain reaction (PCR) were performed on  
 human c-myc oncogene, estrogen receptor gene, and human immunodeficiency virus  
 type 1 long terminal repeat (HIV-1 LTR) gene sequences. The antiproliferative  
 activity of the hybrids was tested in vitro on human myeloid leukemia K562 and  
 T-lymphoid Jurkat cell lines and compared to antiproliferative effects of the  
 natural product distamycin A 1, its tetrapyrrole homolog, DC 81, and a PBD  
 ester. The new hybrids exhibit different DNA-binding activity with respect to  
 both distamycin A 1 and the parent PBD. In addition, a direct relationship  
 was found between the number of pyrrole rings present in the hybrids and the  
 stability of drug/DNA complexes. With respect to antiproliferative effects,  
 it was found that the increase in the length of the polypyrrole backbone leads  
 to an increase of in vitro antiproliferative effects, i.e., the hybrid with 4  
 pyrroles is more active than the other ones both against K562 and Jurkat cell  
 lines.  
 IT 219562-65-9P 256949-59-4P 256949-63-0P  
 256949-64-1P 256949-65-2P 256949-66-3P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (preparation, antiproliferative activity, and DNA-binding  
 pyrrolobenzodiazepines containing oligopyrrole carriers)  
 RN 219562-65-9 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(3-methoxy-3-oxopropoxy)-5-  
 oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



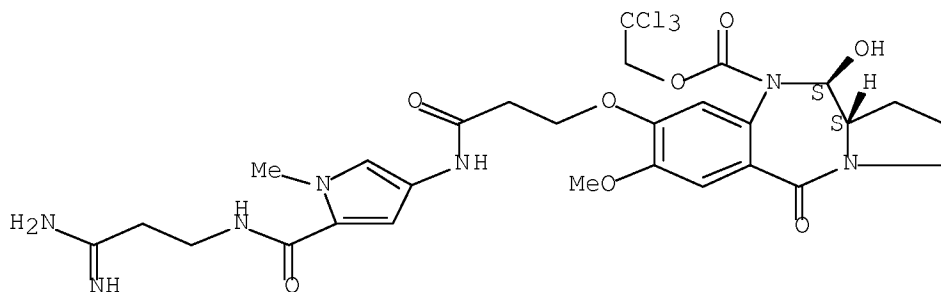
RN 256949-59-4 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
 10-(2,2,2-trichloroethyl) ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 256949-63-0 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-[3-[[5-[[[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
 2,2,2-trichloroethyl ester, monohydrochloride, (11S,11aS)- (9CI) (CA  
 INDEX NAME)

Absolute stereochemistry.



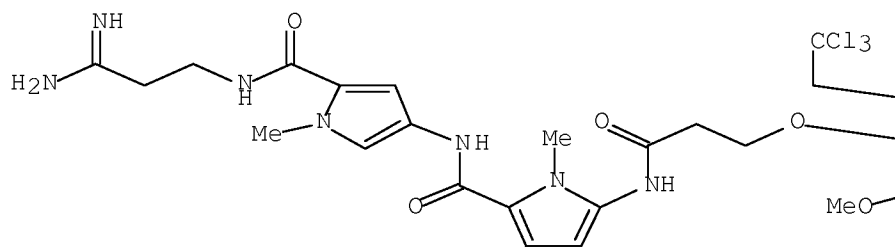
● HCl

RN 256949-64-1 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-[3-[[5-[[[5-[[[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]-3-oxopropoxy]-  
 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl  
 ester, monohydrochloride, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

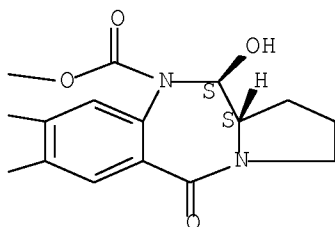


PAGE 1-A



● HCl

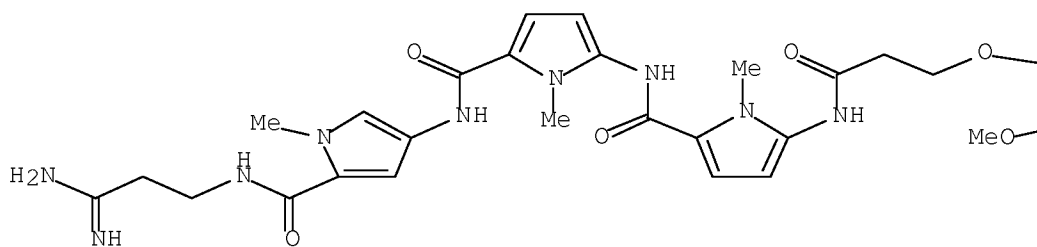
PAGE 1-B



RN 256949-65-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-[3-[[5-[[[5-[[[5-[[3-amino-3-iminopropyl]amino]carbonyl]-1-methyl-1H-  
 pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]carbonyl]-1-  
 methyl-1H-pyrrol-2-yl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-  
 hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, monohydrochloride,  
 (11S,11aS)- (9CI) (CA INDEX NAME)

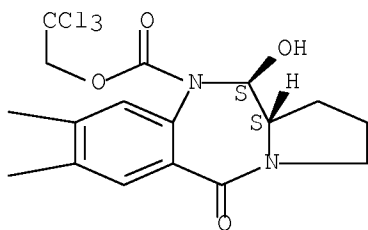
Absolute stereochemistry.

PAGE 1-A



● HCl

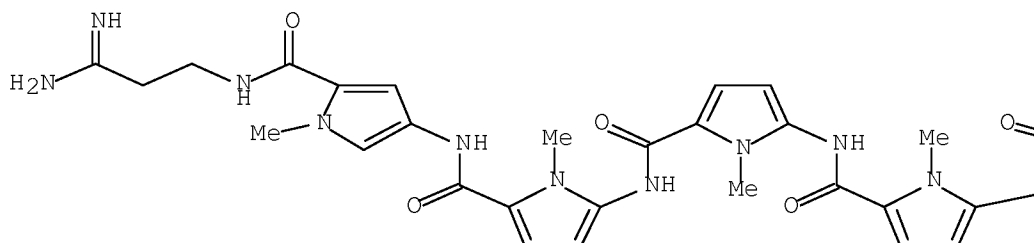
PAGE 1-B



RN 256949-66-3 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-[3-[[5-[[[5-[[[5-[[[5-[[[3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-  
 1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]carbonyl]-1-  
 methyl-1H-pyrrol-2-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]amino]-3-  
 oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
 2,2,2-trichloroethyl ester, monohydrochloride, (11S,11aS)- (9CI) (CA  
 INDEX NAME)

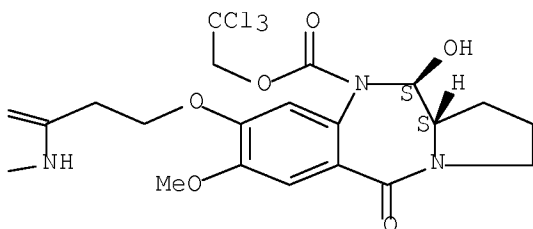
Absolute stereochemistry.

PAGE 1-A



● HCl

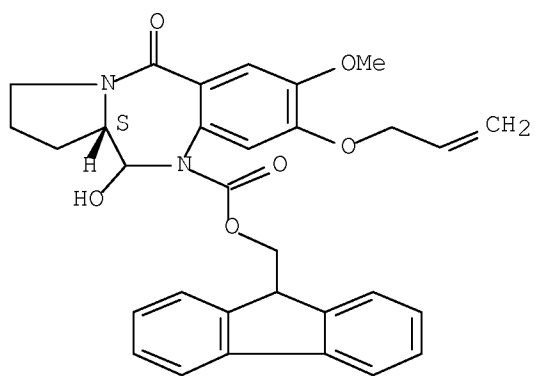
PAGE 1-B



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 34 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1999:583940 CAPLUS Full-text  
 DN 132:89603  
 TI Design, Synthesis, and Evaluation of a Novel Sequence-Selective  
 Epoxide-Containing DNA Cross-Linking Agent Based on the  
 Pyrrolo[2,1-c][1,4]benzodiazepine System  
 AU Wilson, Stuart C.; Howard, Philip W.; Forrow, Stephen M.; Hartley, John  
 A.; Adams, Lesley J.; Jenkins, Terence C.; Kelland, Lloyd R.; Thurston,  
 David E.  
 CS CRC Gene Targeted Drug Design Research Group School of Pharmacy and  
 Biomedical Sciences, University of Portsmouth, Hants., PO1 2DT, UK  
 SO Journal of Medicinal Chemistry (1999), 42(20), 4028-4041  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 132:89603  
 AB Synthetic routes have been investigated to prepare a novel C8-epoxide-  
 functionalized pyrrolo[2,1-c][1,4]benzodiazepine 1 as a potential sequence-  
 selective DNA crosslinking agent (Wilson et al. Tetrahedron Lett. 1995, 36,  
 6333-6336). A successful synthesis was accomplished via a 10-step route  
 involving a pro-N10-Fmoc cleavage method that should have general  
 applicability to other pyrrolbenzodiazepine (PBD) mols. containing acid- or  
 nucleophile-sensitive groups. During the course of this work, a one-pot  
 reductive cyclization procedure for the synthesis of PBD N10-C11 imines from  
 nitro di-Me acetals was also discovered, although this method results in C11a  
 racemization which can reduce DNA binding affinity and cytotoxicity. The  
 target epoxide 1 was shown by thermal denaturation studies to have a  
 significantly higher DNA-binding affinity than the parent DC-81 or the C8-  
 propenoxy-PBD, which is structurally similar but lacks the epoxide moiety.  
 The time course of effects upon thermal denaturation indicated a rapid initial  
 binding phase followed by a slower phase consistent with the stepwise  
 crosslinking of DNA observed for a difunctional agent. This was confirmed by  
 an electrophoretic assay which demonstrated efficient induction of interstrand  
 cross-links in plasmid DNA at concns. >1  $\mu$ M. Higher levels of interstrand  
 crosslinking were observed at 24 h compared to 6 h incubation. A Taq  
 polymerase stop assay indicated a preference for binding to guanine-rich  
 sequences as predicted for bis-alkylation in the minor groove of DNA by  
 epoxide and imine moieties. The pattern of stop sites could be partly  
 rationalized by mol. modeling studies which suggested low-energy models to  
 account for the observed binding behavior. The epoxide PBD 1 was shown to  
 have significant cytotoxicity (45-60 nM) in the A2780, CH1, and CH1cisR human  
 ovarian carcinoma cell lines and an IC50 of 0.2  $\mu$ M in A2780cisR. The  
 significant activity of 1 in the cisplatin-resistant CH1cisR cell line (IC50 =  
 47 nM) gave a resistance factor of 0.8 compared to the parent cell line,  
 demonstrating no cross-resistance with the major groove crosslinking agent  
 cisplatin.  
 IT 251109-29-2P 251109-30-5P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (intermediate; preparation of novel sequence-selective epoxide-containing  
 DNA crosslinking agent based on pyrrolo[2,1-c][1,4]benzodiazepine system)  
 RN 251109-29-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(2-propenyloxy)-,  
 9H-fluoren-9-ylmethyl ester, (11aS)- (9CI) (CA INDEX NAME)

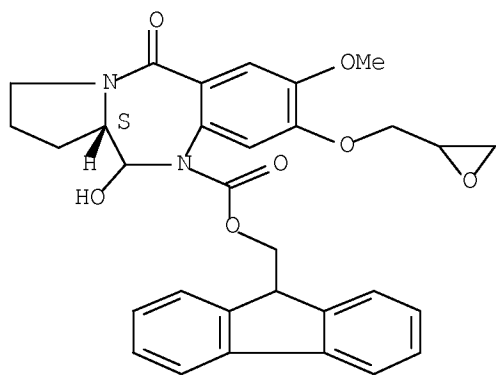
Absolute stereochemistry.



RN 251109-30-5 CAPLUS

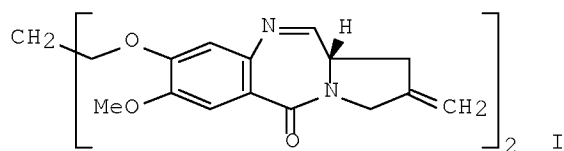
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(oxiranylmethoxy)-5-oxo-,  
9H-fluoren-9-ylmethyl ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



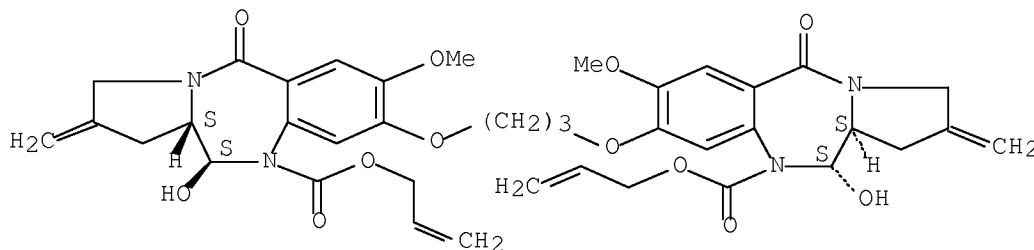
RE.CNT 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 35 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1999:273645 CAPLUS Full-text  
 DN 131:116218  
 TI Synthesis of a novel C2/C2'-exo unsaturated pyrrolobenzodiazepine  
 cross-linking agent with remarkable DNA binding affinity and cytotoxicity  
 AU Gregson, Stephen J.; Howard, Philip W.; Thurston, David E.; Jenkins,  
 Terence C.; Kelland, Lloyd R.  
 CS School of Pharmacy and Biomedical Sciences, CRC Gene Targeted Drug Design  
 Research Group, University of Portsmouth, Portsmouth, Hants, PO1 2DT, UK  
 SO Chemical Communications (Cambridge) (1999), (9), 797-798  
 CODEN: CHCOFS; ISSN: 1359-7345  
 PB Royal Society of Chemistry  
 DT Journal  
 LA English  
 GI



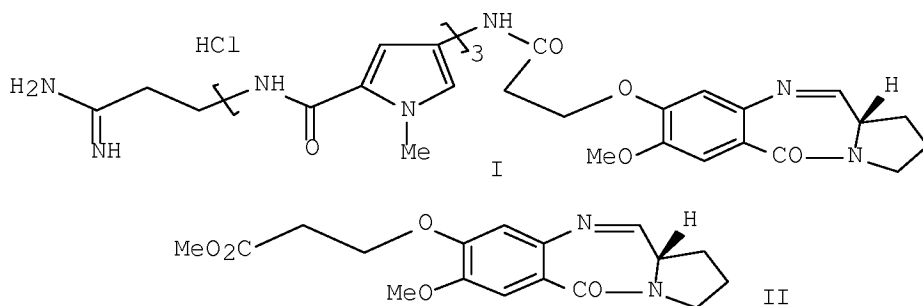
AB A C2/C2'-exo unsatd. pyrrolobenzodiazepine dimer (I) has been synthesized  
 which is cytotoxic at the picomolar level and has remarkable covalent DNA  
 binding affinity, raising the melting temperature of duplex-form calf thymus  
 DNA by 34 after 18 h incubation.  
 IT 232931-64-5P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (preparation DNA binding and cytotoxicity of pyrrolobenzodiazepine  
 crosslinking agents towards ovarian cancer cells)  
 RN 232931-64-5 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
 methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-  
 (9CI) (CA INDEX NAME)

Absolute stereochemistry.



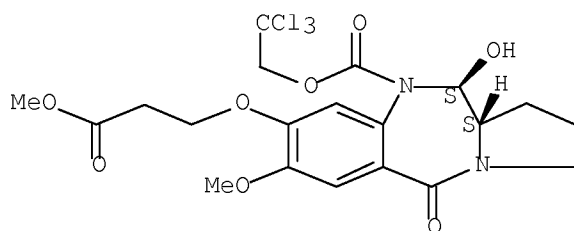
RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 36 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1998:760824 CAPLUS Full-text  
 DN 130:95405  
 TI Design, synthesis and biological activity of a pyrrolo[2,1-  
 c][1,4]benzodiazepine (PBD)-distamycin hybrid  
 AU Baraldi, Pier Giovanni; Cacciari, Barbara; Guiotto, Andrea; Leoni,  
 Alberto; Romagnoli, Romeo; Spalluto, Giampiero; Mongelli, Nicola; Howard,  
 Philip W.; Thurston, David E.; Bianchi, Nicoletta; Gambari, Roberto  
 CS Dipartimento di Scienze Farmaceutiche, Universita di Ferrara, Ferrara,  
 44100, Italy  
 SO Bioorganic & Medicinal Chemistry Letters (1998), 8(21), 3019-3024  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Science Ltd.  
 DT Journal  
 LA English  
 OS CASREACT 130:95405  
 GI



AB The authors report the synthesis of a new hybrid (I) which is a combination of the naturally occurring antitumor agent distamycin A and the pyrrolo[2,1-c][1,4]benzodiazepine (II), related to naturally occurring anthramycin. The antitumor activity of the hybrid I was tested in vitro and compared to the natural product distamycin A and the PBD II.  
 IT 219562-65-9P 219562-76-2P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (design, synthesis and biol. activity of a pyrrolo[2,1-c][1,4]benzodiazepine (PBD)-distamycin hybrid)  
 RN 219562-65-9 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(3-methoxy-3-oxopropoxy)-5-oxo-, 2,2,2-trichloroethyl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

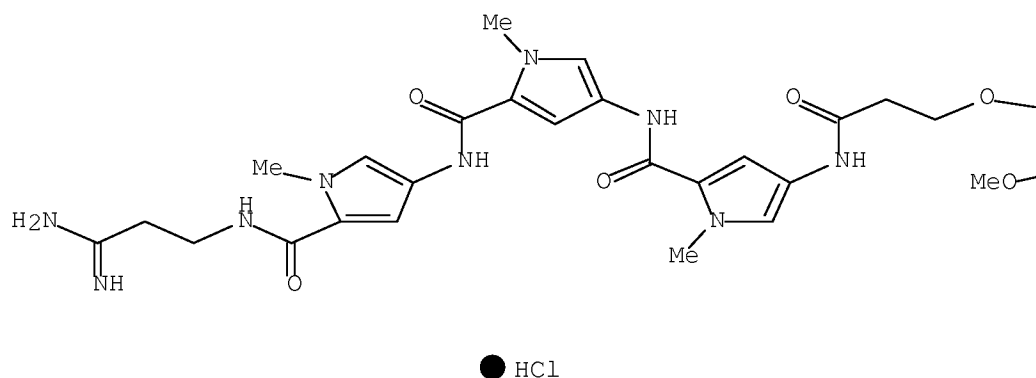


RN 219562-76-2 CAPLUS

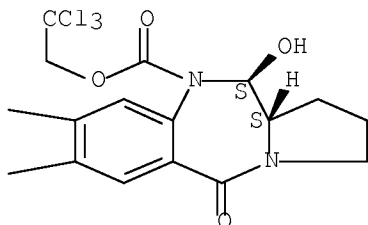
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[3-[[5-[[[5-[[[5-[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-3-oxopropoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2,2,2-trichloroethyl ester, monohydrochloride, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



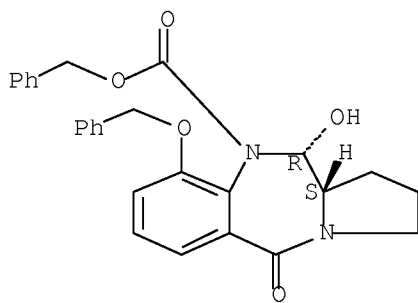
PAGE 1-B



RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 37 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1998:595149 CAPLUS Full-text  
 DN 129:290006  
 TI Stereoselective Synthesis of Tilivalline  
 AU Nagasaka, Tatsuo; Koseki, Yuji  
 CS School of Pharmacy, Tokyo University of Pharmacy and Life Science, Tokyo,  
 192-0392, Japan  
 SO Journal of Organic Chemistry (1998), 63(20), 6797-6801  
 CODEN: JOCEAH; ISSN: 0022-3263  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 129:290006  
 AB Tilivalline, a metabolite from *Klebsiella pneumoniae* var. *ocytoca*, was easily  
 synthesized in five steps from (S)-proline and 3-(benzyloxy)isatoic anhydride.  
 This synthesis is based on modified Curtius reactions of 3-substituted  
 phthalic anhydrides to 3-substituted isatoic anhydrides, conversion of lactams  
 to the acyliminium precursors, and stereoselective introduction of indole from  
 the less hindered side.  
 IT 214277-31-3P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (stereoselective synthesis of tilivalline)  
 RN 214277-31-3 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-5-oxo-9-(phenylmethoxy)-, phenylmethyl  
 ester, (11R,11aS)- (CA INDEX NAME)

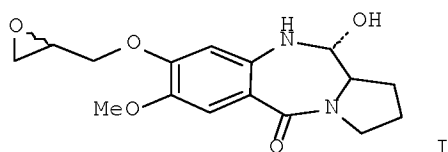
Absolute stereochemistry. Rotation (+).



RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

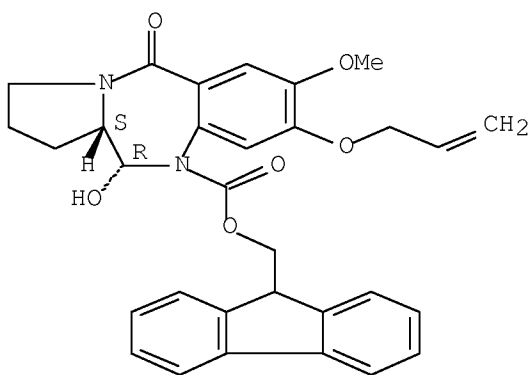


L11 ANSWER 38 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1996:247427 CAPLUS Full-text  
 DN 125:33599  
 TI Design and synthesis of a novel epoxide-containing pyrrolo[2,1-  
 c][1,4]benzodiazepine (PBD) via a new cyclization procedure  
 AU Wilson, Stuart C.; Howard, Philip W.; Thurston, David E.  
 CS Sch. Pharm. Biomed. Sci., Univ. Portsmouth, Portsmouth, Hants., PO1 2DZ,  
 UK  
 SO Electronic Conference on Trends in Organic Chemistry [CD-ROM] (1996),  
 Meeting Date 1995, Paper 32. Editor(s): Rzepa, Henry S.; Leach,  
 Christopher; Goodman, Jonathan M. Publisher: Royal Society of Chemistry,  
 Cambridge, UK.  
 CODEN: 62TKAB  
 DT Conference  
 LA English  
 GI



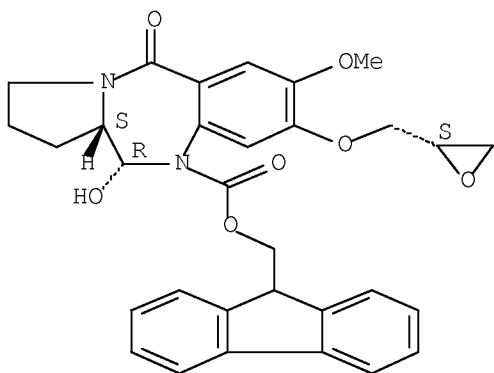
AB The synthesis of potential DNA-crosslinking pyrrolo[2,1- c][1,4]benzodiazepine  
 I, substituted at C-8 with a 2,3-epoxypropaneoxy moiety, via a new cyclization  
 procedure is described.  
 IT 177569-43-6P 177569-44-7P 177569-45-8P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (design and synthesis of a novel epoxide-containing pyrrolobenzodiazepine  
 via new cyclization procedure)  
 RN 177569-43-6 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(2-propenyloxy)-,  
 9H-fluoren-9-ylmethyl ester, (11R-trans)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



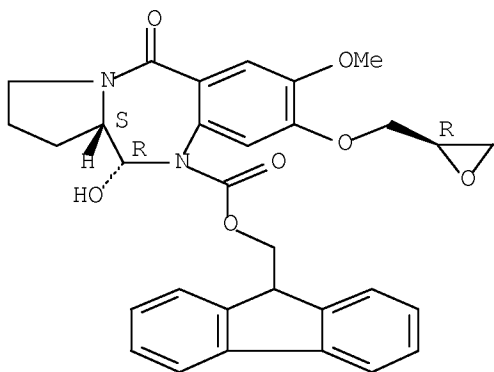
RN 177569-44-7 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(oxiranylmethoxy)-5-oxo-,  
 9H-fluoren-9-ylmethyl ester, [11R-[8(S\*),11 $\alpha$ ,11a $\beta$ ]]- (9CI) (CA  
 INDEX NAME)

Absolute stereochemistry.

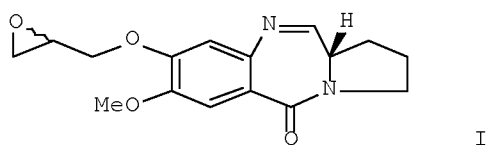


RN 177569-45-8 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(oxiranylmethoxy)-5-oxo-,  
 9H-fluoren-9-ylmethyl ester, [11R-[8(R\*),11 $\alpha$ ,11a $\beta$ ]]- (9CI) (CA  
 INDEX NAME)

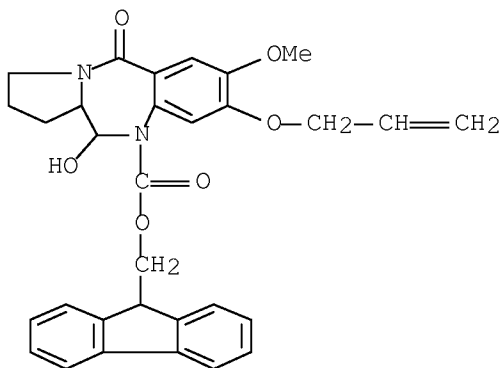
Absolute stereochemistry.



L11 ANSWER 39 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1995:786320 CAPLUS Full-text  
 DN 124:8772  
 OREF 124:1853a,1856a  
 TI Design and synthesis of a novel epoxide-containing pyrrolo[2,1-c][1,4]benzodiazepine (PBD) via a new cyclization procedure  
 AU Wilson, Stuart C.; Howard, Philip W.; Thurston, David E.  
 CS Div. Med. Chem., Univ. Portsmouth, Portsmouth, Hants., PO1 2DZ, UK  
 SO Tetrahedron Letters (1995), 36(35), 6333-6  
 CODEN: TELEAY; ISSN: 0040-4039  
 PB Elsevier  
 DT Journal  
 LA English  
 OS CASREACT 124:8772  
 GI

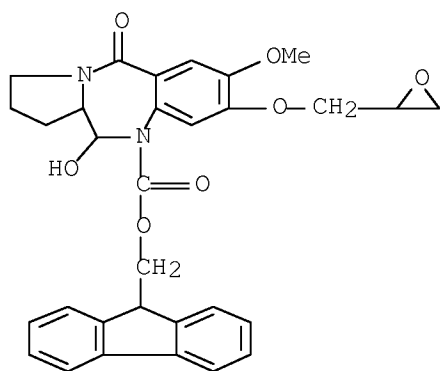


AB The synthesis of a potential DNA-crosslinking pyrrolo[2,1-c][1,4]benzodiazepine I substituted at the C8-position with a 2,3-epoxypropaneoxy moiety using a new cyclization procedure is described.  
 IT 171002-57-6P 171002-58-7P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (design and synthesis of a novel epoxide-containing pyrrolobenzodiazepine via a new cyclization procedure)  
 RN 171002-57-6 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(2-propenyloxy)-, 9H-fluoren-9-ylmethyl ester (9CI) (CA INDEX NAME)

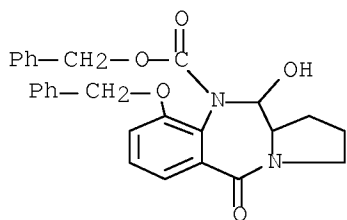


RN 171002-58-7 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,

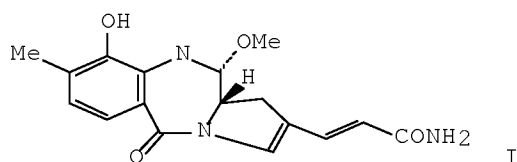
2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-8-(oxiranylmethoxy)-5-oxo-,  
9H-fluoren-9-ylmethyl ester (9CI) (CA INDEX NAME)



L11 ANSWER 40 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1995:730623 CAPLUS Full-text  
 DN 123:227886  
 OREF 123:40699a,40702a  
 TI A stereoselective synthesis of tilivalline and its analogs utilizing a new  
 Mannich type intramolecular cyclization  
 AU Aoyama, Toyohiko; Shioiri, Takayuki  
 CS Fac. Pharm. Sci., Nagoya City Univ., Nagoya, 467, Japan  
 SO Yakugaku Zasshi (1995), 115(6), 446-59  
 CODEN: YKKZAJ; ISSN: 0031-6903  
 PB Pharmaceutical Society of Japan  
 DT Journal  
 LA Japanese  
 OS CASREACT 123:227886  
 AB Tilivalline (I), a metabolite isolated from *Klebsiella pneumoniae* var.  
 oxytoca, belongs to a group of pyrrolo[2,1-c][1,4]benzodiazepines, a  
 characteristic skeleton of anthramycin-type antitumor antibiotics. The  
 authors have accomplished a completely stereoselective, efficient and  
 convenient synthesis of I utilizing a new Mannich type intramol. cyclization  
 as a key step. Further, a computational chemical anal. clarified the effect  
 of zinc chloride on the high stereoselectivity in the tilivalline synthesis.  
 To aim both the extension of the scope of the new Mannich type intramol.  
 cyclization and the studies on the structure-biol. activity relationship, the  
 authors further extended the method to the synthesis of tilivalline derivs.  
 and 2-(3'-indolyl)-1,4-benzodiazepines. Investigation on the cytotoxicity of I  
 and its analogs has revealed that I shows the strong cytotoxicity toward mouse  
 leukemia L 1210 cells and the replacement of the indole function of I with  
 cyano one increases the cytotoxicity of I about 100 times (IC<sub>50</sub> = 0.05 µg/mL).  
 IT 125299-57-2P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (stereoselective synthesis of tilivalline and analogs utilizing a new  
 Mannich type intramol. cyclization)  
 RN 125299-57-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-5-oxo-9-(phenylmethoxy)-, phenylmethyl  
 ester (CA INDEX NAME)

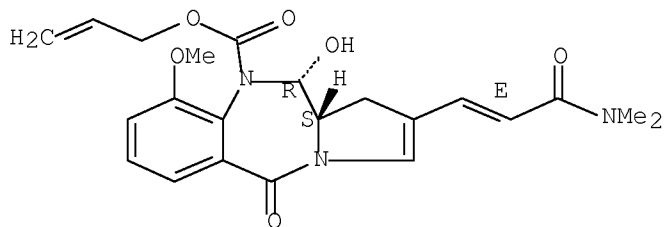


L11 ANSWER 41 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1993:472411 CAPLUS Full-text  
 DN 119:72411  
 OREF 119:13045a,13048a  
 TI Total synthesis of (+)-porothramycin B  
 AU Fukuyama, Tohru; Liu, Gang; Linton, Steven D.; Lin, Shao Cheng; Nishino, Hiroshi  
 CS Dep. Chem., Rice Univ., Houston, TX, 77251, USA  
 SO Tetrahedron Letters (1993), 34(16), 2577-80  
 CODEN: TELEAY; ISSN: 0040-4039  
 DT Journal  
 LA English  
 GI

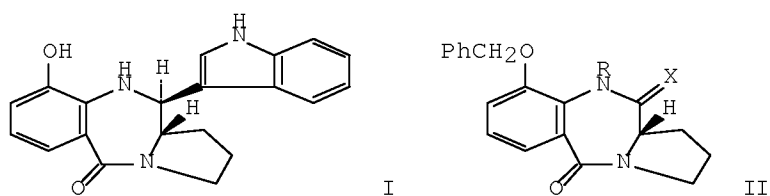


AB The first total synthesis of (+)-porothramycin B (I), starting from L-glutamic acid, is described. The synthetic pathway can be readily applied to the synthesis of other members of the pyrrolo[1,4]benzodiazepine antibiotics.  
 IT 148680-25-5F  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and catalytic hydrogenation of)  
 RN 148680-25-5 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2-[3-(dimethylamino)-3-oxo-1-propenyl]-11,11a-dihydro-11-hydroxy-9-methoxy-5-oxo-, 2-propenyl ester, [2(E),11 $\alpha$ ,11 $\beta$ ]-(+)- (9CI) (CA INDEX NAME)

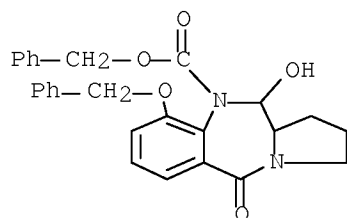
Rotation (+). Absolute stereochemistry unknown.  
 Double bond geometry as shown.



L11 ANSWER 42 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1990:98950 CAPLUS Full-text  
 DN 112:98950  
 OREF 112:16843a,16846a  
 TI Stereoselective synthesis of tilivalline  
 AU Nagasaka, Tatsuo; Koseki, Yuji; Hamaguchi, Fumiko  
 CS Tokyo Coll. Pharm., Hachioji, 192-03, Japan  
 SO Tetrahedron Letters (1989), 30(14), 1871-2  
 CODEN: TELEAY; ISSN: 0040-4039  
 DT Journal  
 LA English  
 OS CASREACT 112:98950  
 GI



AB Tilivalline (I) was easily synthesized by converting lactam II (X = O, R = H) to the acyliminium precursor II (X = H,HO, R = PhCH<sub>2</sub>O<sub>2</sub>C), followed by stereoselectively introducing indole from the less hindered side of II (X = H,HO, R = PhCH<sub>2</sub>O<sub>2</sub>C).  
 IT 125299-57-2F  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation and condensation of, with indole)  
 RN 125299-57-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 2,3,11,11a-tetrahydro-11-hydroxy-5-oxo-9-(phenylmethoxy)-, phenylmethyl  
 ester (CA INDEX NAME)



L11 ANSWER 43 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN

AN 1988:621909 CAPLUS Full-text

DN 109:221909

OREF 109:36521a,36524a

TI Pyrrolo[1,4]benzodiazepine antitumor antibiotics: relationship of DNA alkylation and sequence specificity to the biological activity of natural and synthetic compounds

AU Hurley, Laurence H.; Reck, Teri; Thurston, David E.; Langley, David R.; Holden, Kenneth G.; Hertzberg, Robert P.; Hoover, John R. E.; Gallagher, Gregory, Jr.; Faucette, Leo F.; et al.

CS Coll. Pharm., Univ. Texas, Austin, TX, 78712, USA

SO Chemical Research in Toxicology (1988), 1(5), 258-68  
CODEN: CRTOEC; ISSN: 0893-228X

DT Journal

LA English

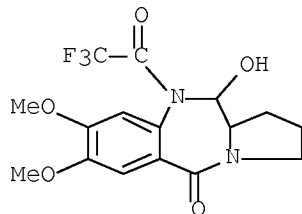
AB The DNA alkylation and sequence specificity of a group of natural and synthetic pyrrolo[1,4]benzodiazepines [P(1,4)Bs] were evaluated by using an exonuclease III stop assay, and the results were compared with in vitro and in vivo biol. potency and antitumor activity. The P(1,4)B antibiotics are potent antitumor agents produced by various Actinomycetes, which are believed to mediate their cytotoxic effects by covalent bonding through N-2 of guanine in the minor groove of DNA. The results of a sensitive DNA alkylation assay using exonuclease III that permits both estimation of the extent of DNA modification as well as location of the precise guanines to which the drugs are covalently bound are described. Using this assay, a series of natural and synthetic compds. of the P(1,4)B class was evaluated for their ability to bond to DNA; also their DNA sequence preference was determined. The compds. included are P(1,4)Bs carrying different substituents in the aromatic ring, having varying degrees of saturation in the 5-membered ring, or differing in the stereochem. at C-11a. These same compds. were evaluated for in vitro cytotoxic activity against B16 melanoma cells, for potency in vivo in B6D2F1 mice (LD50), and for antitumor activity (ILSmax) against P388 leukemia cells. A good correlation was found between extent of DNA bonding and in vitro and in vivo potency. Furthermore, on the basis of electronic and steric considerations, it was possible to rationalize why those compds. that showed negligible biol. activity were unable to bond covalently to DNA. The degree of saturation in the five-membered ring of the P(1,4)Bs had a significant effect on the DNA bonding reactivity and biol. activity of this class of compds.

IT 116564-87-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation and deacylation-methylation of)

RN 116564-87-5 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-11-hydroxy-7,8-dimethoxy-10-(trifluoroacetyl)- (9CI) (CA INDEX NAME)





L11 ANSWER 44 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN

AN 1981:139855 CAPLUS Full-text

DN 94:139855

OREF 94:22905a,22908a

TI Benzodiazepines

PA Green Cross Corp., Japan

SO Belg., 24 pp.

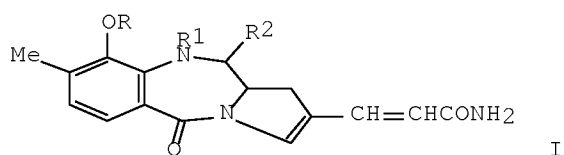
CODEN: BEXXAL

DT Patent

LA French

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	----	-----	-----	-----
PI	BE 882305	A1	19800716	BE 1980-199851	19800319
	JP 56015289	A	19810214	JP 1979-89886	19790717
	JP 62037631	B	19870813		
	SE 8001458	A	19810118	SE 1980-1458	19800225
	SE 436882	B	19850128		
	SE 436882	C	19850509		
	CA 1152985	A1	19830830	CA 1980-346511	19800227
	US 4309437	A	19820105	US 1980-127984	19800304
	GB 2053894	A	19810211	GB 1980-8033	19800310
	GB 2053894	B	19830420		
	NL 8001531	A	19810120	NL 1980-1531	19800314
	DE 3010544	A1	19810129	DE 1980-3010544	19800319
	DE 3010544	C2	19820701		
	FR 2461711	A1	19810206	FR 1980-6153	19800319
	FR 2461711	B1	19830513		
	CH 648848	A5	19850415	CH 1980-2187	19800320
PRAI	JP 1979-89886	A	19790717		
OS	MARPAT 94:139855				
GI					



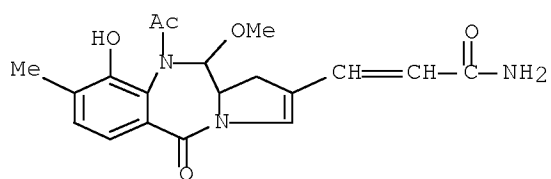
AB Pyrrolobenzodiazepines I (R = H, acyl, CONH<sub>2</sub>, alkoxycarbonyl; R<sub>1</sub> = H, acyl; R<sub>2</sub> = SO<sub>2</sub>H) were prepared by treating I (R<sub>2</sub> = OMe) with Na dithionite. I (R<sub>2</sub> = SO<sub>3</sub>H) were prepared by oxidizing I (R<sub>2</sub> = SO<sub>2</sub>H) or by treating I (R<sub>2</sub> = OMe) with SO<sub>2</sub> or K<sub>2</sub>SO<sub>3</sub>. Thus, 1 g I (R = R<sub>1</sub> = Ac, R<sub>2</sub> = OMe) was treated with Na dithionite to give 0.8 g I (R = R<sub>1</sub> = Ac, R<sub>2</sub> = SO<sub>2</sub>H), which at 0.12 mg/kg daily i.p. for 6 days increased the survival time of leukemia P388 infected mice by 190%.

IT 77004-92-3 77004-94-5 77004-97-8

RL: RCT (Reactant); RACT (Reactant or reagent)  
(sulfinatation of)

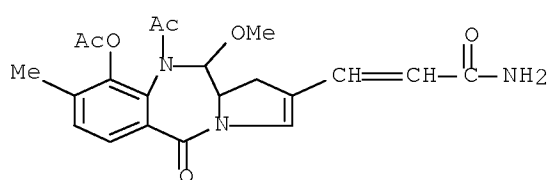
RN 77004-92-3 CAPLUS

CN 2-Propenamide, 3-(10-acetyl-5,10,11,11a-tetrahydro-9-hydroxy-11-methoxy-8-methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl)- (CA INDEX NAME)



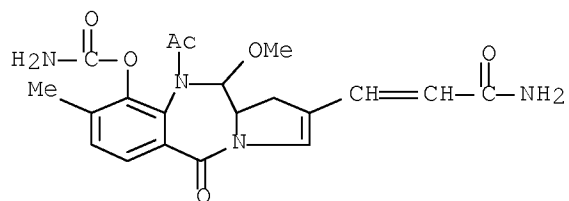
RN 77004-94-5 CAPLUS

CN 2-Propenamide, 3-[10-acetyl-9-(acetyloxy)-5,10,11,11a-tetrahydro-11-methoxy-8-methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]- (CA INDEX NAME)



RN 77004-97-8 CAPLUS

CN 2-Propenamide, 3-[10-acetyl-9-[(aminocarbonyl)oxy]-5,10,11,11a-tetrahydro-11-methoxy-8-methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]- (CA INDEX NAME)



L11 ANSWER 45 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN

AN 1980:51709 CAPLUS Full-text

DN 92:51709

OREF 92:8431a,8434a

TI Antitumor antibiotics. XVI. Molecular mechanism of binding of pyrrolo(1,4)benzodiazepine antitumor agents to deoxyribonucleic acid. Anthramycin and tomaymycin

AU Lown, J. William; Joshua, Alummoottil V.

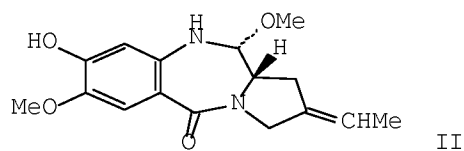
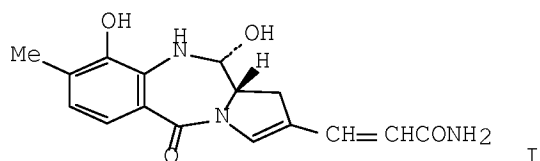
CS Dep. Chem., Univ. Alberta, Edmonton, AB, T6G 2G2, Can.

SO Biochemical Pharmacology (1979), 28(13), 2017-26  
CODEN: BCPCA6; ISSN: 0006-2952

DT Journal

LA English

GI



AB The extent of binding of the pyrrolo[1,4]benzodiazepine antibiotics, anthramycin (I) [4803-27-4] and tomaymycin (II) [35050-55-6], to DNA, measured by suppression of ethidium fluorescence, was proportional to the antibiotic concentration and was partly reversed by a heat-denaturation-renaturation cycle. The extent of binding of I and II to DNA was promoted by lower pH (4.7-9) and higher temps. (0-51°), and the DNA-antibiotic complex was stable to dialysis. There was no evidence that these antibiotics intercalate into DNA, but they were more reactive toward relaxed PM2-DNA than to supercoiled DNA. Examination of DNA binding of the antibiotics and their analogs to DNAs of different base composition and sep. in conjugation with sequence specific binding agents showed little base preference for binding. Reaction of the antibiotics with DNA produced neither depurination nor strand scission. A free or potential carbinolamine or imine function at the 10,11 positions in a benzo[1,4]diazepine nucleus was an absolute requirement for DNA binding or of reaction with nucleophiles.

IT 72521-70-1

RL: BIOL (Biological study)

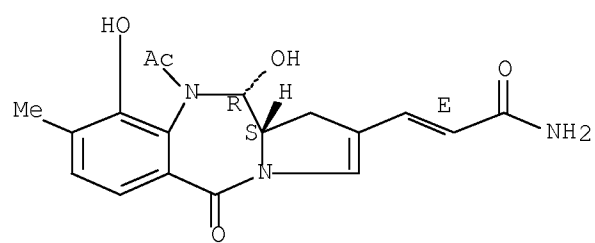
(DNA binding to, mol. mechanism of, structure in relation to)

RN 72521-70-1 CAPLUS

CN 2-Propenamide, 3-(10-acetyl-5,10,11,11a-tetrahydro-9,11-dihydroxy-8-methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl)-, [11R-[2(E),11 $\alpha$ ,11 $\beta$ ]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.



L11 ANSWER 46 OF 46 CAPLUS COPYRIGHT 2008 ACS on STN

AN 1970:531049 CAPLUS Full-text

DN 73:131049

OREF 73:21357a,21360a

TI Antiprotozoal, anthelmintic, and antitumor benzodiazepine compounds

IN Leimgruber, Willy; Schenker, Fausto E.

PA Hoffmann-La Roche Inc.

SO U.S., 13 pp.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	----	-----	-----	-----
PI	US 3523941	A	19700811	US 1967-620618	19670306
PRAI	US 1967-620618	A	19670306		

GI For diagram(s), see printed CA Issue.

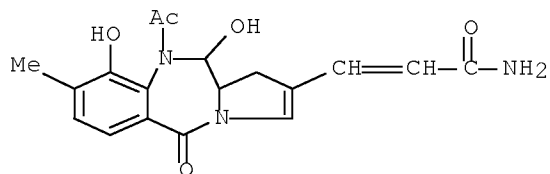
AB The acetates of I and II were prepared by acylation of the corresponding 9-OH derivative I (R1 = R2 = H, R3 =  $\alpha$ -OMe) (III), or its hydrate. The epimers of I were prepared by acylating III, removing the elements of MeOH from the mol. by an 8 hr reflux with H2C:C(Me)OAc and treating the product with MeOH at room temperature. Thus, III in 1:1 Ac2O-NEt3 stirred 4 hr at 20° gave (11R,11aS)-5,10,11,11a-tetrahydro-9-hydroxy-11-methoxy-8-methyl-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-2-trans-acrylamide acetate (IV). (11S,11aS)-Epimer of IV was similarly prepared and had the same activity against S 180 and Ehrlich solid tumors in mice. II (R1 = H) stirred 2 hr at 20° in 1:1 Ac2O-C5H5N gave II (R1 = Ac) (V). V in 4:1 H2O-Me2CO kept 18 hr at 20° gave I (R1 = H, R2 = Ac, R3 = OH) (VI). V in C5H5N kept 3 days at 20° in AcOH-Ac2O gave I (R1 = R2 = Ac, R3 = AcO). Treatment of III.H2O with (EtCO)2O-NEt3, (PrCO)2O-NEt2, or Bz3O-NEt3 gave I (R1 = EtCO, PrCO, or Bz). Similar acylations of III.H2O with PhNCO, EtNCO, or (EtO)2CO in the presence of NEt3 gave I (R1 = PhNHCO, EtNHCO, EtCO2). I are useful as antitumor agents against Sarcoma 180 and Ehrlich solid tumors in mice, as antiprotozoal agents against Entamoeba histolytica and Trichomonas vaginalis, and as anthelmintic agents against Syphacia obvelata.

IT 29455-45-6P 29455-46-7P 29455-48-9P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of)

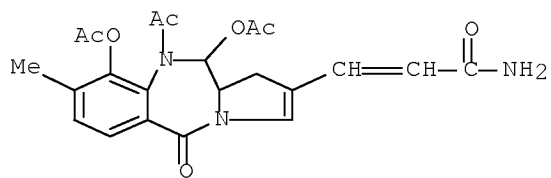
RN 29455-45-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acrylamide, 10-acetyl-5,10,11,11a-tetrahydro-9,11-dihydroxy-8-methyl-5-oxo-, (E)-(S,S)-(+)-(8CI) (CA INDEX NAME)



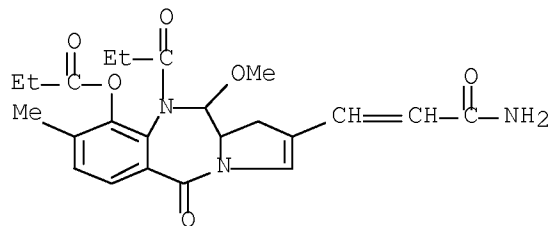
RN 29455-46-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acrylamide, 10-acetyl-5,10,11,11a-tetrahydro-9,11-dihydroxy-8-methyl-5-oxo-, diacetate (ester), (E)-(S,S)-(+)-(8CI) (CA INDEX NAME)



RN 29455-48-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acrylamide, 5,10,11,11a-tetrahydro-9-hydroxy-11-methoxy-8-methyl-5-oxo-10-propionyl-, propionate (ester), (E)-(11R,11aS)- (8CI) (CA INDEX NAME)



L18 ANSWER 1 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2008:502670 CAPLUS Full-text

TI Humanized anti-human CD38 antibodies and conjugates for diagnosis and treatment of cancer, asthma, autoimmune disease and inflammation

IN Park, Peter U.; Bartle, Laura M.; Skaletskaya, Anna; Golmakher, Viktor S.; Tavares, Daniel; Deckert, Jutta; Mikol, Vincent; Blanc, Veronique

PA Sanofi-Aventis, Fr.

SO PCT Int. Appl., 133pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 2008047242	A2	20080424	WO 2007-IB4172	20071016
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
	RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	EP 1914242	A1	20080423	EP 2006-291628	20061019
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				

PRAI EP 2006-291628 A 20061019

AB Antibodies, humanized antibodies, resurfaced antibodies, antibody fragments, derivatized antibodies, and conjugates of same with cytotoxic agents, which specifically bind to CD38, are capable of killing CD38+ cells by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and/or complement-dependent cytotoxicity (CDC). Said antibodies and fragments thereof may be used in the treatment of tumors that express CD38 protein, such as multiple myeloma, chronic lymphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, or acute lymphocytic leukemia, or the treatment of autoimmune and inflammatory diseases such as systemic lupus, rheumatoid arthritis, multiple sclerosis, erythematosus, and asthma. Said derivatized antibodies may be used in the diagnosis and imaging of tumors that express elevated levels of CD38. Also provided are cytotoxic conjugates comprising a cell binding agent and a cytotoxic agent, therapeutic compns. comprising the conjugate, methods for using the conjugates in the inhibition of cell growth and the treatment of disease, and a kit comprising the cytotoxic conjugate. In particular, the cell binding agent is a monoclonal antibody, and epitope-binding fragments thereof, that recognizes and binds the CD38 protein.

IT 877659-86-4 945489-85-0 945489-86-1  
945489-88-3 945489-89-4 945489-90-7  
945489-91-8 945489-95-2 945490-00-6  
945490-04-0 945490-10-8 945490-12-0  
945490-23-3 945490-31-3 945490-37-9  
945490-40-4 945490-42-6 945490-46-0  
945490-54-0 945490-59-5 945490-63-1  
945490-67-5 945490-71-1 945490-76-6  
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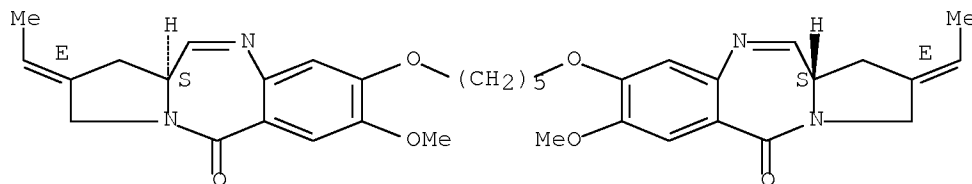
RL: DGN (Diagnostic use); MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(humanized anti-human CD38 antibodies and conjugates for diagnosis and treatment of cancer, asthma, autoimmune disease and inflammation)

RN 877659-86-4 CAPLUS

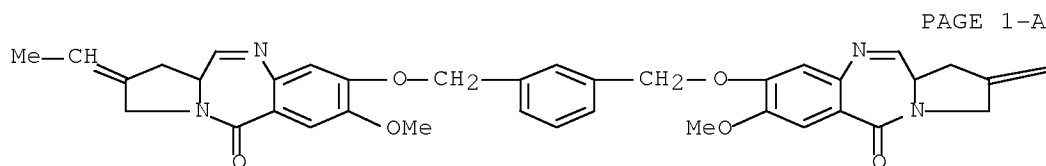
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediy]bis(oxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.



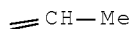
RN 945489-85-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-phenylenebis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)



PAGE 1-A

PAGE 1-B



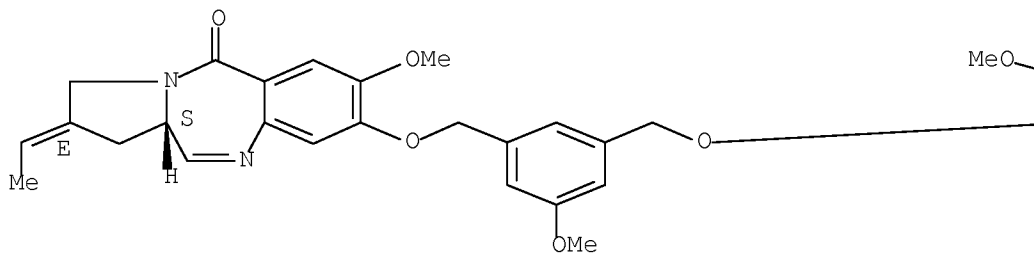
RN 945489-86-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[(5-methoxy-1,3-phenylene)bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

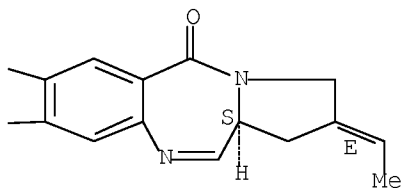
Absolute stereochemistry.  
Double bond geometry as shown.



PAGE 1-A

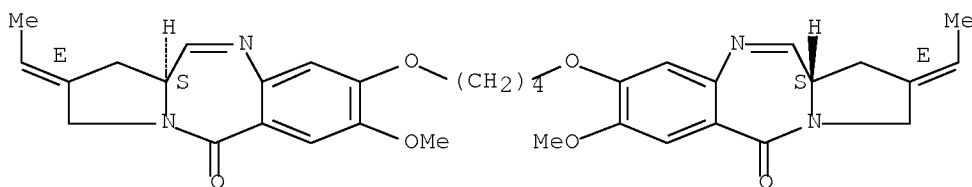


PAGE 1-B



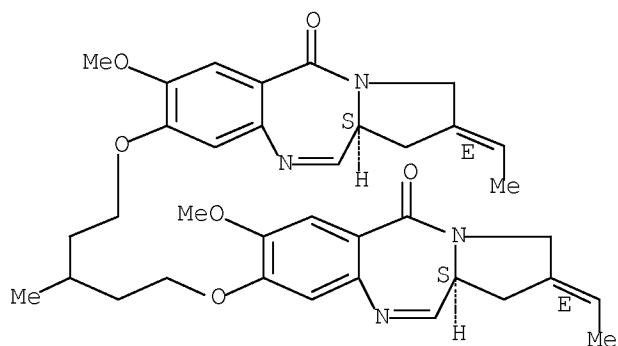
RN 945489-88-3 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as shown.



RN 945489-89-4 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[(3-methyl-1,5-pentanediy1)bis(oxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

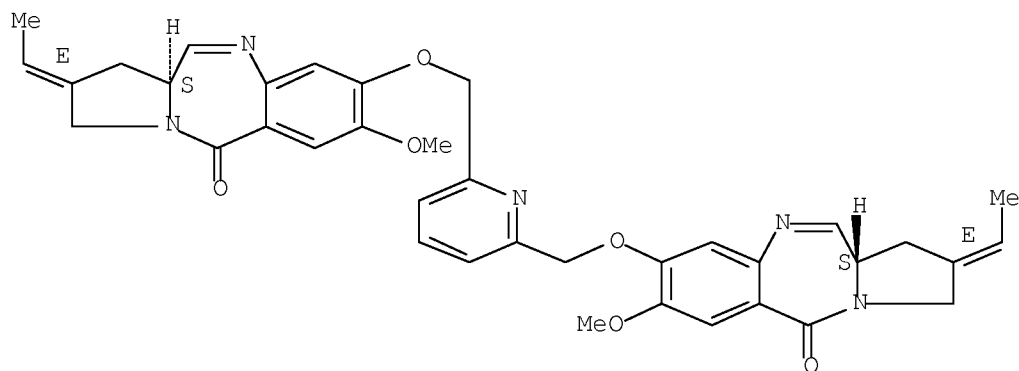
Absolute stereochemistry.  
 Double bond geometry as shown.



RN 945489-90-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[2,6-pyridinediylbis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

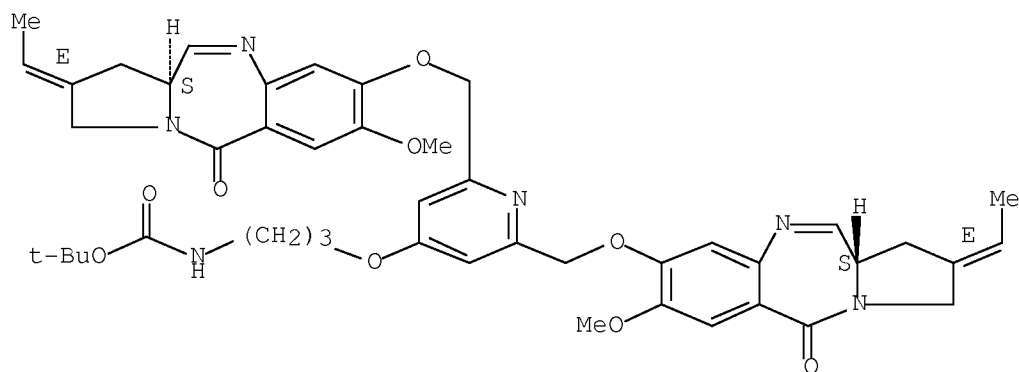
Absolute stereochemistry.  
Double bond geometry as shown.



RN 945489-91-8 CAPLUS

CN Carbamic acid, N-[3-[[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]-4-pyridinyl]oxy]propyl]-, 1,1-dimethylethyl ester (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

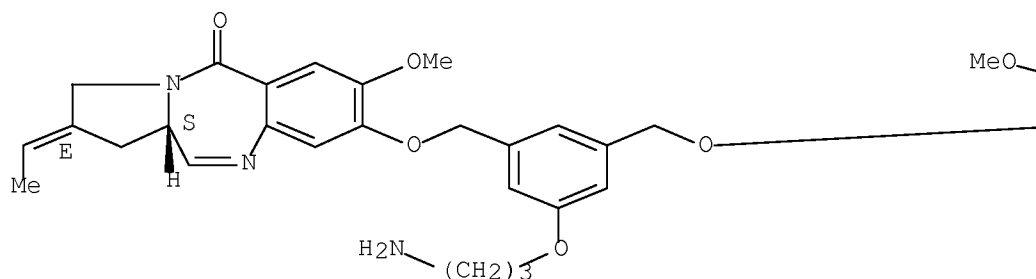


RN 945489-95-2 CAPLUS

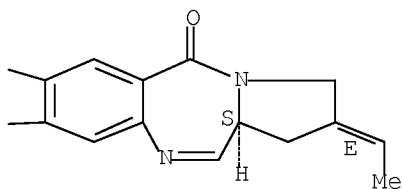
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[5-(3-aminopropoxy)-1,3-phenylene]bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

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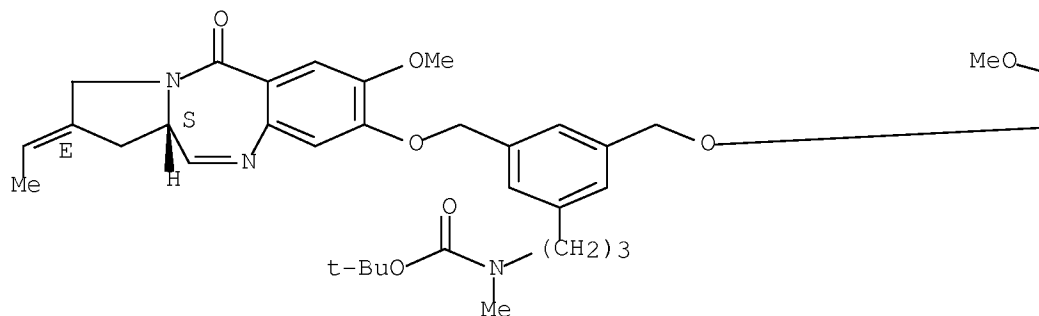


RN 945490-00-6 CAPLUS

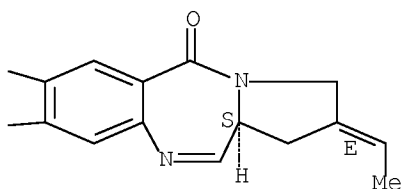
CN Carbamic acid, N-[3-[3,5-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenyl]propyl]-N-methyl-, 1,1-dimethylethyl ester (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A



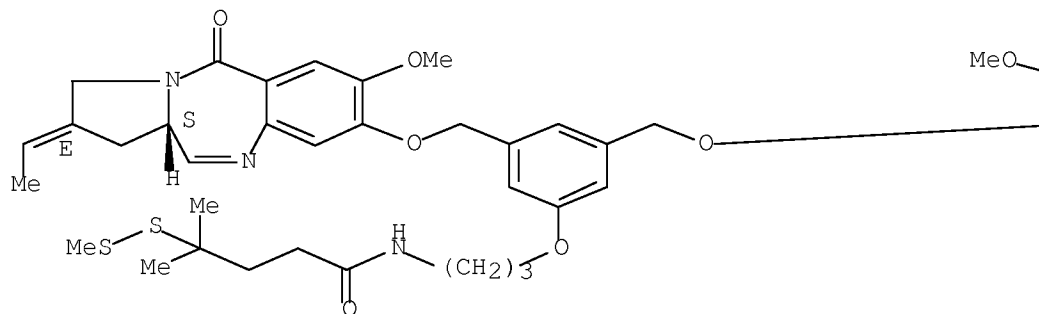
PAGE 1-B

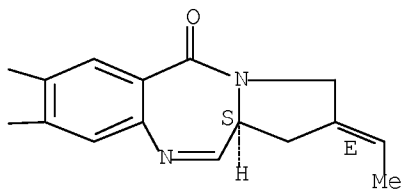


RN 945490-04-0 CAPLUS  
CN Pentanamide, N-[3-[3,5-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenoxy]propyl]-4-methyl-4-(methyldithio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A

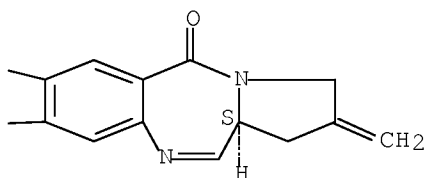
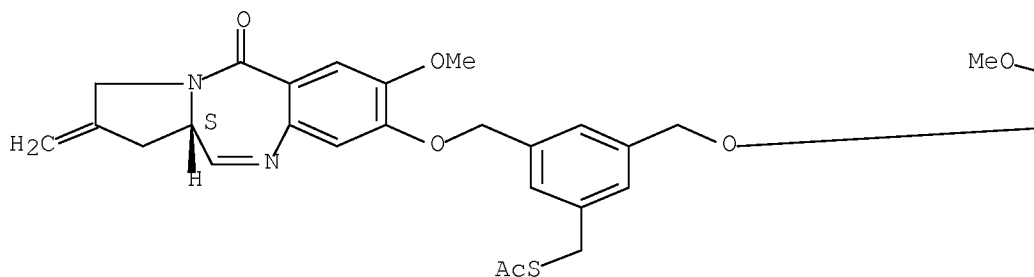




RN 945490-10-8 CAPLUS

CN Ethanethioic acid, S-[[3,5-bis[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenyl]methyl] ester (CA INDEX NAME)

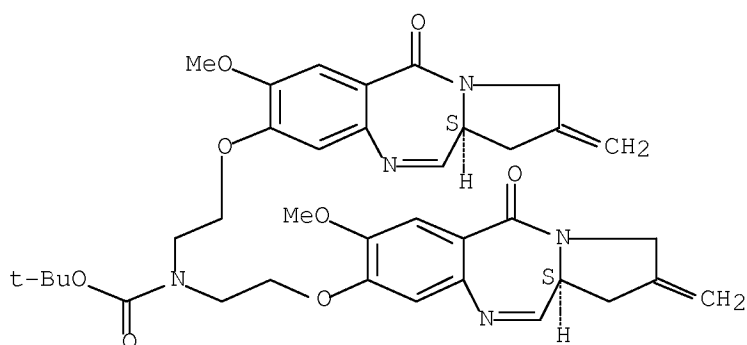
Absolute stereochemistry.



RN 945490-12-0 CAPLUS

CN Carbamic acid, N,N-bis[2-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]ethyl]-, 1,1-dimethylethyl ester (CA INDEX NAME)

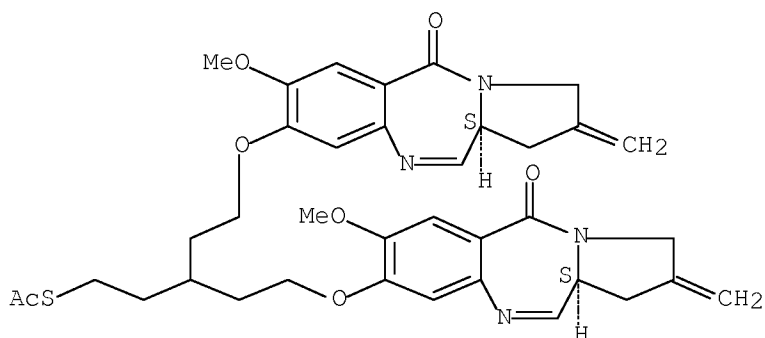
Absolute stereochemistry.



RN 945490-23-3 CAPLUS

CN Ethanethioic acid, S-[5-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-3-[2-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]ethyl]pentyl] ester (CA INDEX NAME)

Absolute stereochemistry.



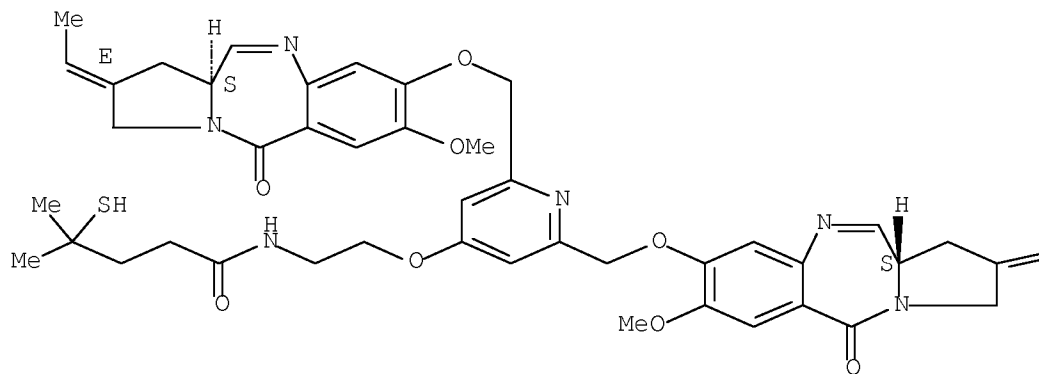
RN 945490-31-3 CAPLUS

CN Pentanamide, N-[2-[[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]-4-pyridinyl]oxy]ethyl]-4-mercapto-4-methyl- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.

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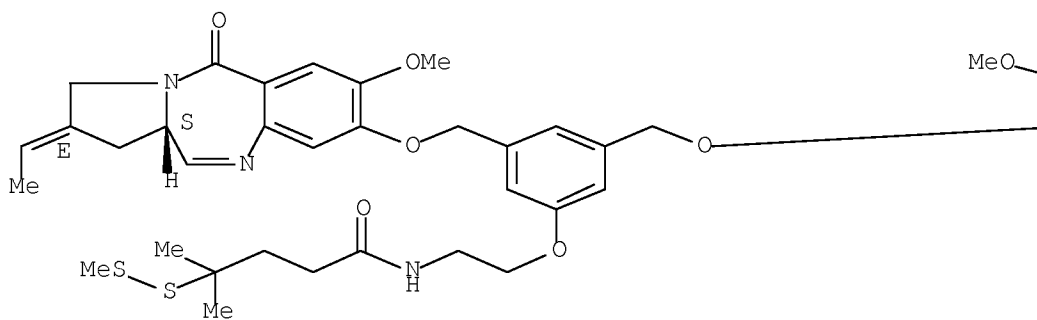
PAGE 1-B

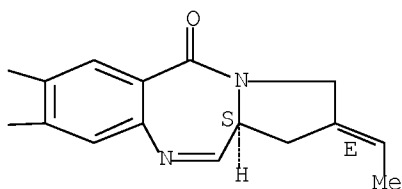


RN 945490-37-9 CAPLUS  
 CN Pentanamide, N-[2-[3,5-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenoxy]ethyl]-4-methyl-4-(methyldithio)- (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as shown.

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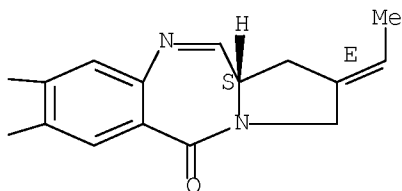
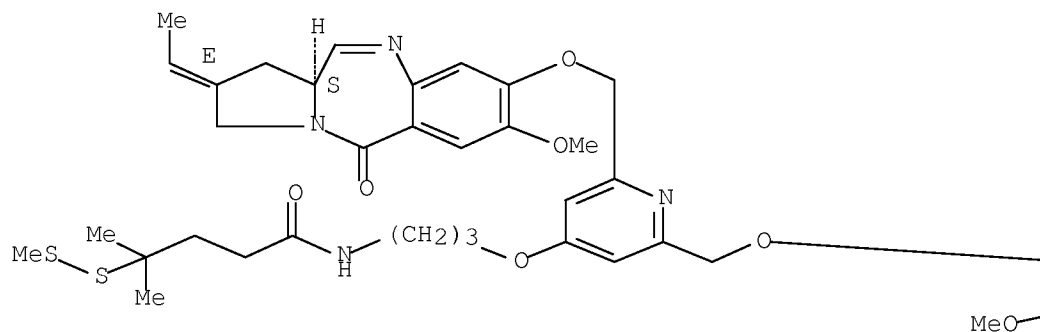




RN 945490-40-4 CAPLUS

CN Pentanamide, N-[3-[[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]-4-pyridinyl]oxy]propyl]-4-methyl-4-(methyldithio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.



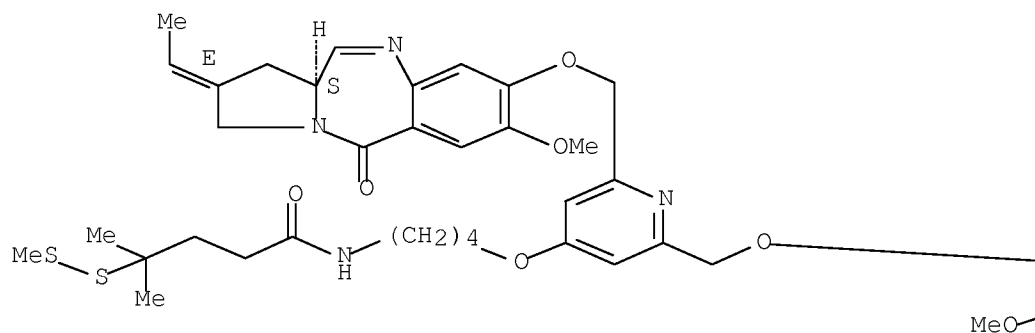
RN 945490-42-6 CAPLUS



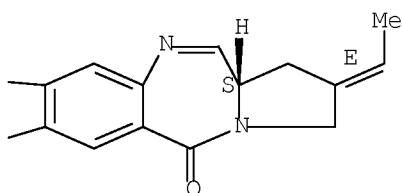
CN Pentanamide, N-[4-[[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]-4-pyridinyl]oxy]butyl]-4-methyl-4-(methylthio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

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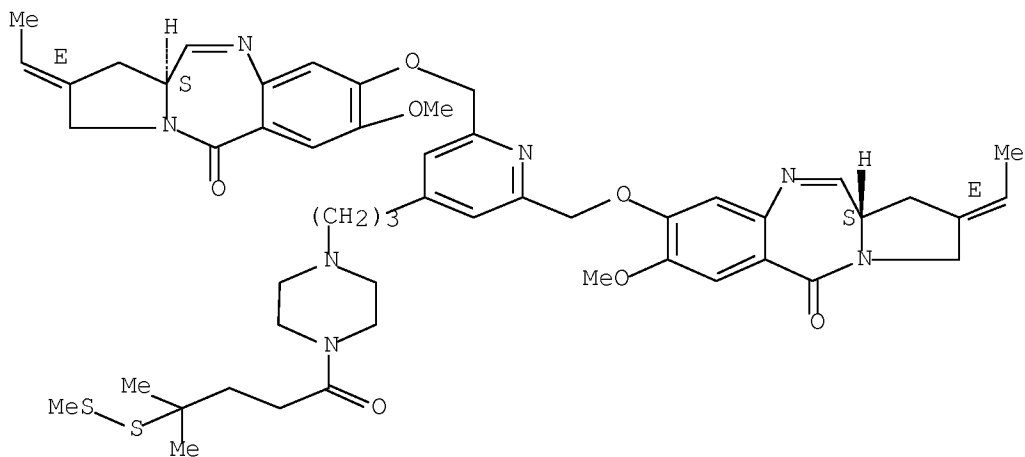


PAGE 1-B



RN 945490-46-0 CAPLUS  
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[4-[3-[4-[4-methyl-4-(methylthio)-1-oxopentyl]-1-piperazinyl]propyl]-2,6-pyridinediyl]bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

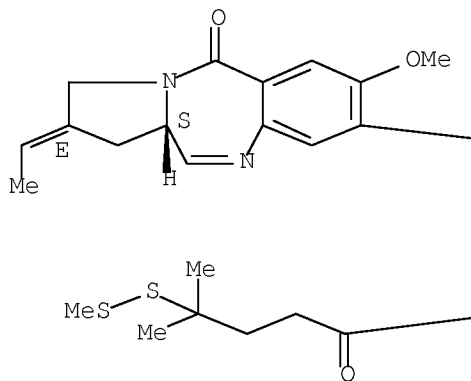


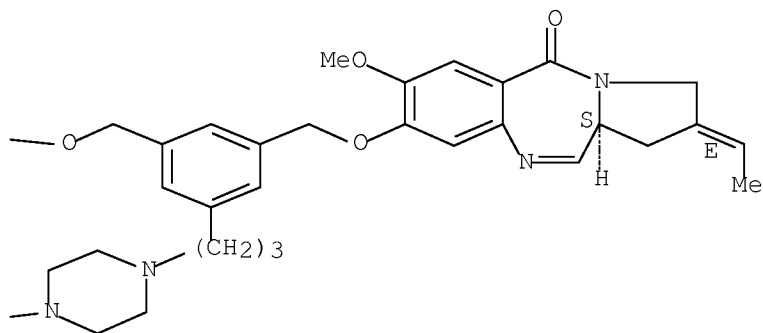
RN 945490-54-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[5-[3-[4-[4-methyl-4-(methylthio)-1-oxopentyl]-1-piperazinyl]propyl]-1,3-phenylene]bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

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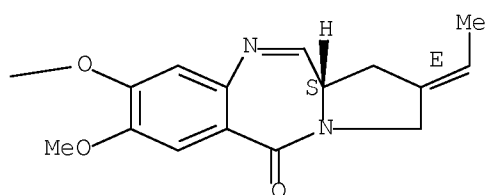
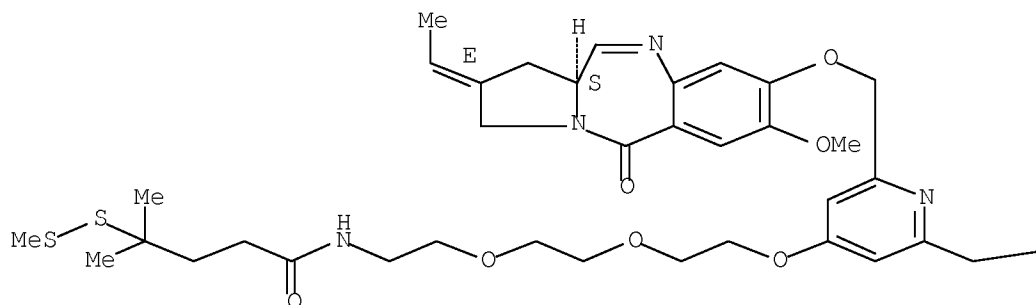




RN 945490-59-5 CAPLUS

CN Pentanamide, N-[2-[2-[2-[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]-4-pyridinyl]oxy]ethoxy]ethoxy]ethyl]-4-methyl-4-(methylthio)- (CA INDEX NAME)

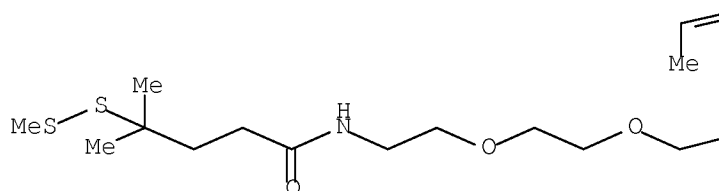
Absolute stereochemistry.  
Double bond geometry as shown.



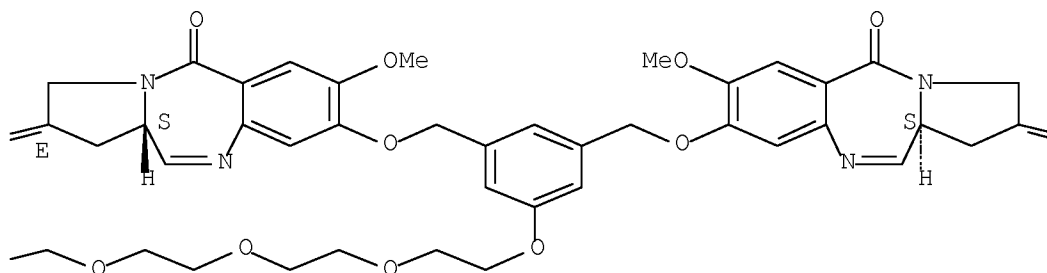
RN 945490-63-1 CAPLUS  
 CN Pentanamide, N-[17-[3,5-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenoxy]-3,6,9,12,15-pentaoxaheptadec-1-yl]-4-methyl-4-(methylthio)- (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as shown.

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PAGE 1-C

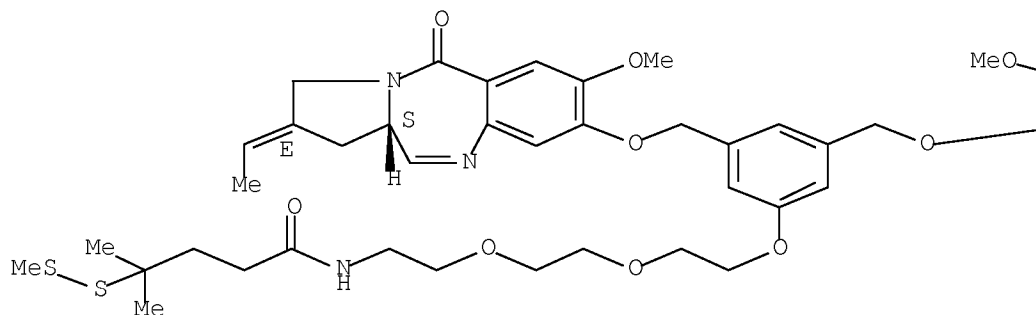


RN 945490-67-5 CAPLUS  
 CN Pentanamide, N-[2-[2-[2-[3,5-bis[[[(2E,11aS)-2-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-

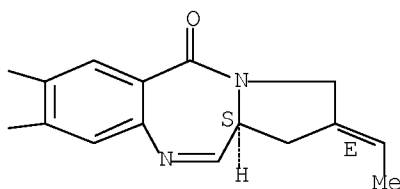
yl]oxy)methyl]phenoxy]ethoxy]ethoxy]ethyl]-4-methyl-4-(methyldithio)- (CA  
INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

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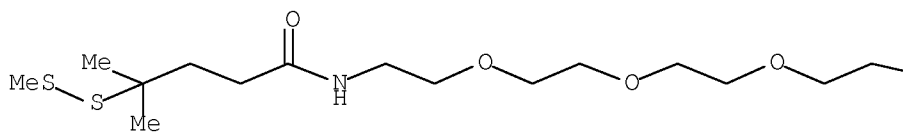
PAGE 1-B

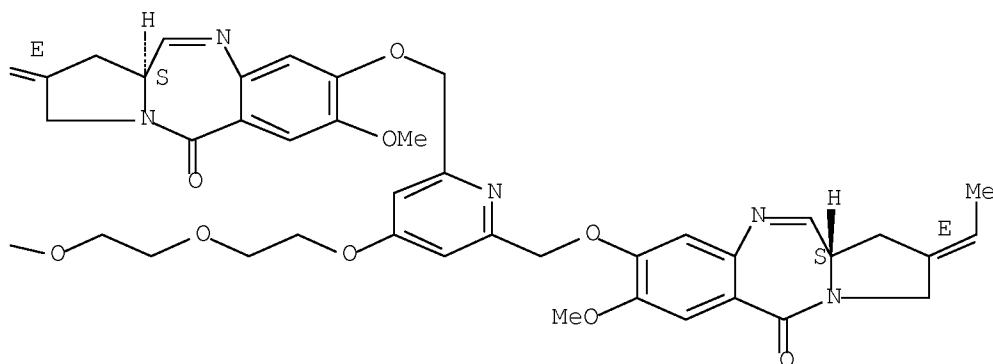


RN 945490-71-1 CAPLUS  
CN Pentanamide, N-[17-[[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy)methyl]-4-pyridinyl]oxy]-3,6,9,12,15-pentaoxaheptadec-1-yl]-4-methyl-4-(methyldithio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

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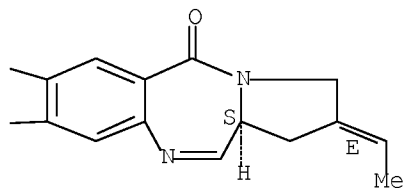
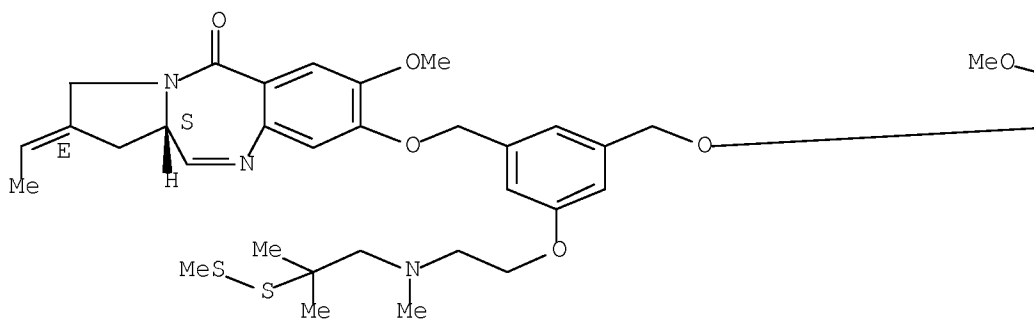




RN 945490-76-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[5-[2-[methyl[2-methyl-2-(methyldithio)propyl]amino]ethoxy]-1,3-phenylene]bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

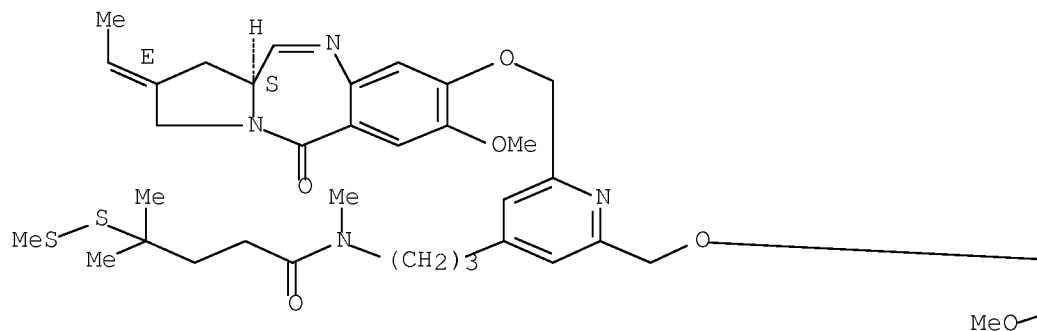
Absolute stereochemistry.  
Double bond geometry as shown.



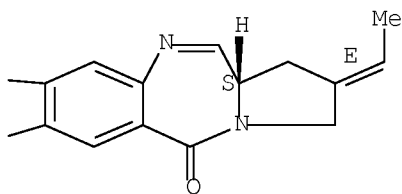
RN 945490-80-2 CAPLUS  
 CN Pentanamide, N-[3-[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy)methyl]-4-pyridinyl]propyl]-N,4-dimethyl-4-(methyldithio)- (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as shown.

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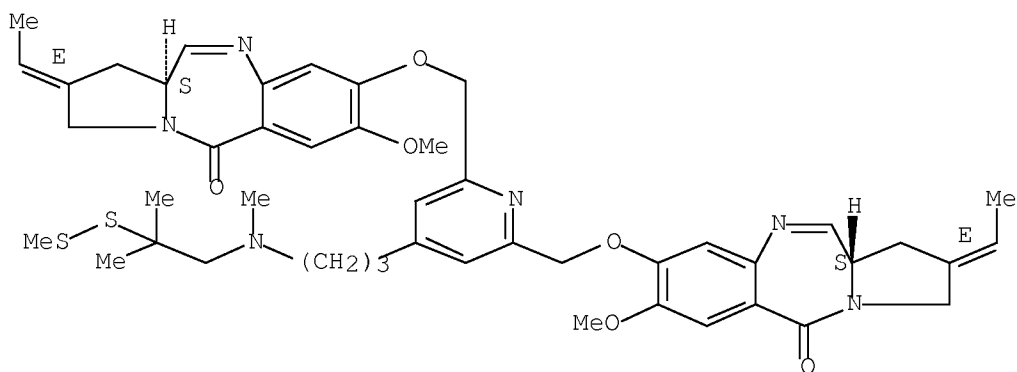


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RN 945490-85-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[4-[3-[methyl[2-methyl-2-(methyldithio)propyl]amino]propyl]-2,6-pyridinediyl]bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as shown.

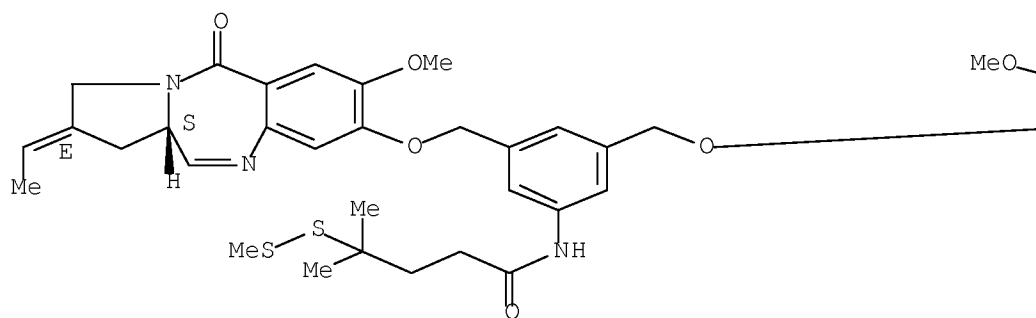


RN 945490-88-0 CAPLUS

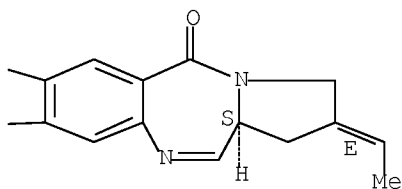
CN Pentanamide, N-[3,5-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenyl]-4-methyl-4-(methylthio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

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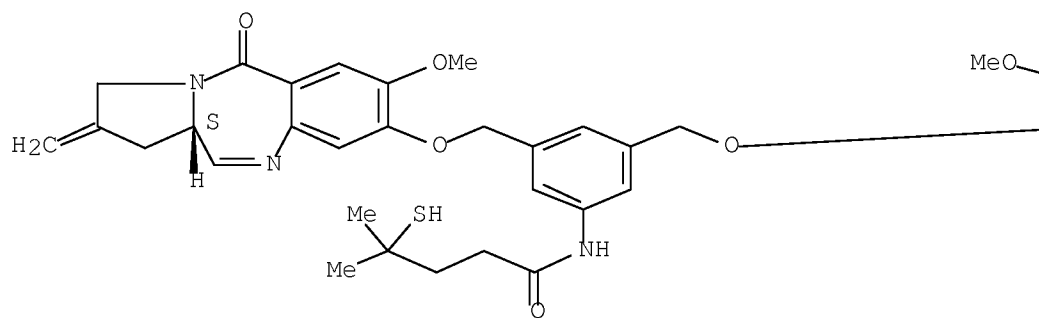
RN 1001321-52-3 CAPLUS

CN Pentanamide, N-[3,5-bis[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenyl]-4-mercapto-4-methyl- (CA INDEX NAME)

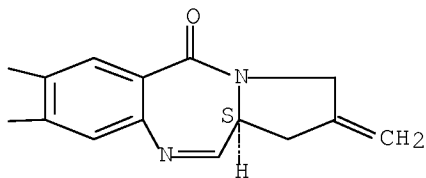


Absolute stereochemistry.

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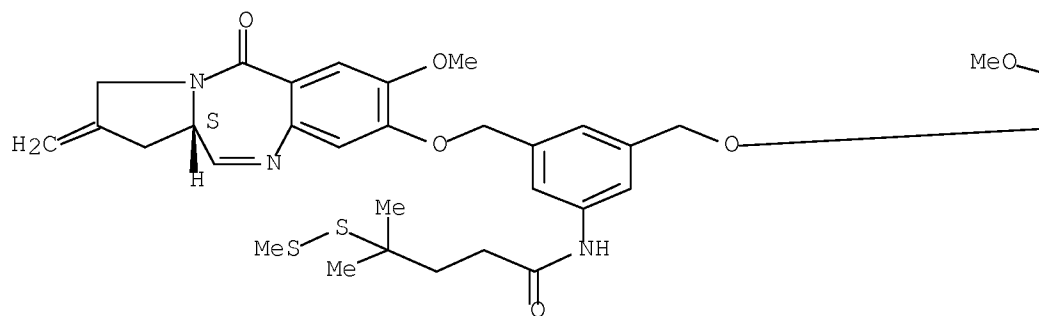
PAGE 1-B

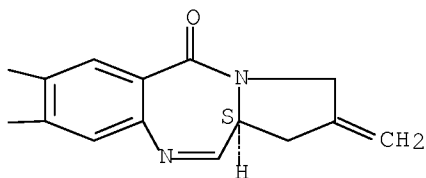


RN 1001321-53-4 CAPLUS  
CN Pentanamide, N-[3,5-bis[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenyl]-4-methyl-4-(methylthio)- (CA INDEX NAME)

Absolute stereochemistry.

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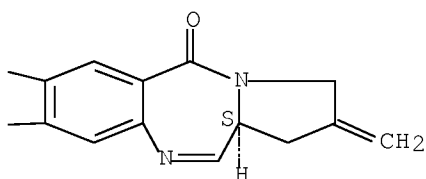
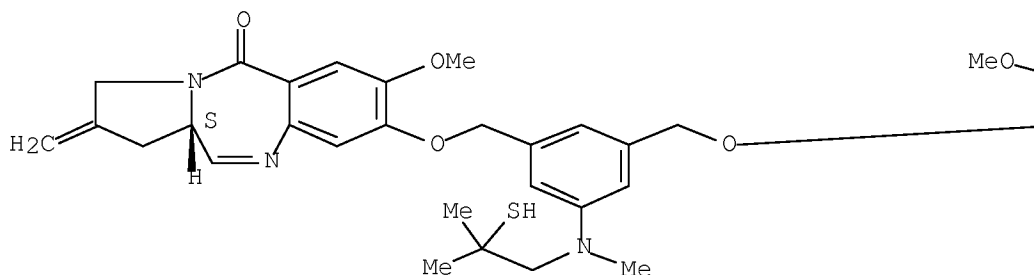




RN 1001321-54-5 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[5-[(2-mercapto-2-methylpropyl)methylamino]-1,3-phenylene]bis(methyleneoxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.

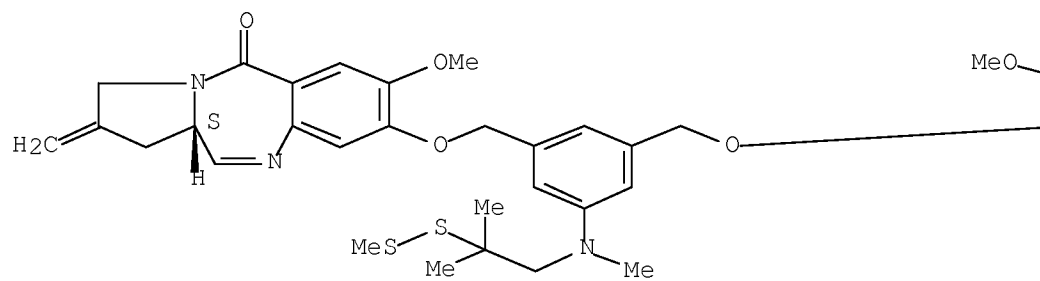


RN 1001321-55-6 CAPLUS

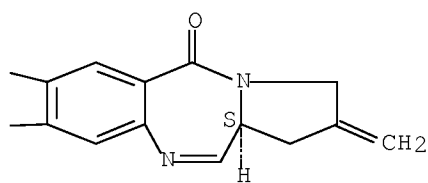
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[5-[methyl[2-methyl-2-(methylthio)propyl]amino]-1,3-phenylene]bis(methyleneoxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.

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L18 ANSWER 2 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2008:285086 CAPLUS Full-text  
 DN 148:347284  
 TI Prediction of an agent's or agents' activity across different cells and  
 tissue types  
 IN Theodorescu, Dan; Lee, Jae Kyun  
 PA USA  
 SO PCT Int. Appl., 124pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2008027912	A2	20080306	WO 2007-US77022	20070828
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

PRAI US 2006-840644P P 20060828  
 US 2006-840834P P 20061122

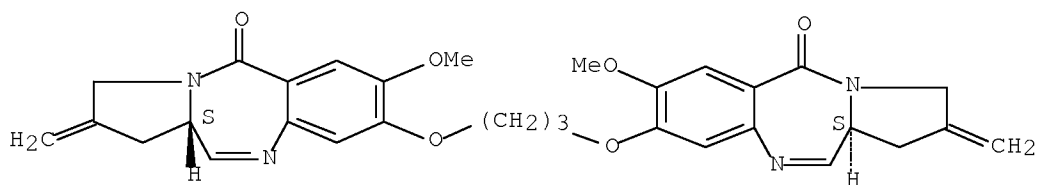
AB The present invention relates to a novel algorithm that uses mol. profile  
 signatures to extrapolate the physiol. processes of one type of cell set  
 (e.g., cell line, tissue, normal or diseased) to predict the activity of an  
 agent or agents against another type of cell set that has never been exposed  
 to the agent in question (drug efficacy prediction). The novel algorithm also  
 allows one to predict the therapeutic response of a patient to a therapeutic  
 regimen even though the patient (or patients) may have never been exposed to  
 that agent before, thereby allowing for selecting a therapeutic agent or  
 combination of agents that would best suit the patient (i.e., personalized  
 medicine). The present invention also relates to methods of using the agents  
 identified by the novel algorithm to treat a variety of diseases, including  
 cancer.

IT 232931-57-6, NSC 694501 763125-64-0, NSC 724005  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (prediction of an agent's or agents' activity across different cells  
 and tissue types for treatment of diseases such as cancer)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
 propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-,  
 (11aS,11'aS)- (CA INDEX NAME)

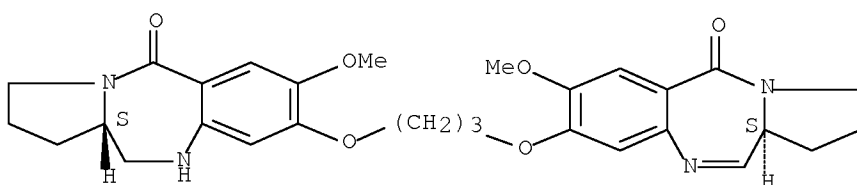
Absolute stereochemistry. Rotation (+).



RN 763125-64-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-7-methoxy-8-[3-[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry.



L18 ANSWER 3 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2008:152576 CAPLUS Full-text

DN 148:403188

TI A facile intramolecular azido/amido reductive cyclization approach:  
synthesis of pyrrolobenzodiazepines and their dimers

AU Kamal, Ahmed; Shankaraiah, N.; Markandeya, N.; Reddy, K. Laxma; Reddy, Ch.  
Sanjeeva

CS Biotransformation Laboratory, Division of Organic Chemistry, Indian  
Institute of Chemical Technology, Hyderabad, 500 007, India

SO Tetrahedron Letters (2008), 49(9), 1465-1468  
CODEN: TELEAY; ISSN: 0040-4039

PB Elsevier Ltd.

DT Journal

LA English

AB A new synthetic pathway was developed for the preparation of imine-containing  
pyrrolo[2,1-c][1,4]benzodiazepines (PBDs) and their dimers. Selective  
reduction of aromatic azides as well as aliphatic amides in a single step  
leading to an intramol. reductive cyclization process by employing LiAlH<sub>4</sub> or  
LiBH<sub>4</sub> provides the cyclized imines.

IT 140676-21-7P 145325-56-0P 145325-57-1P

RL: SPN (Synthetic preparation); PREP (Preparation)

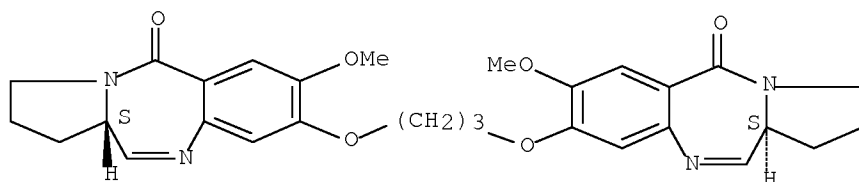
(preparation of pyrrolobenzodiazepines and their dimers by selective  
reduction

of aromatic azides and aliphatic amides and reductive cyclization)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
(CA INDEX NAME)

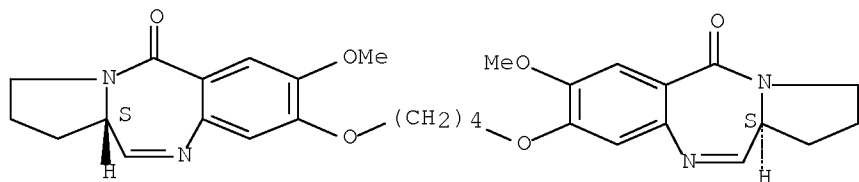
Absolute stereochemistry. Rotation (+).



RN 145325-56-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-  
butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA  
INDEX NAME)

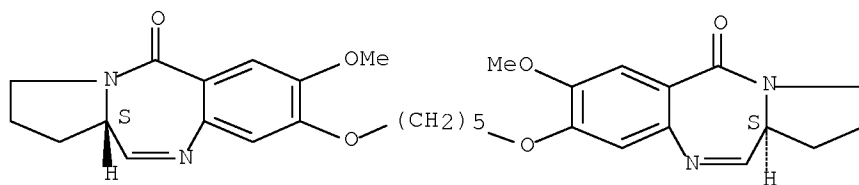
Absolute stereochemistry.



RN 145325-57-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediy]bis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 4 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2008:148261 CAPLUS Full-text

DN 148:370678

TI An assay combining high-performance liquid chromatography and mass spectrometry to measure DNA interstrand cross-linking efficiency in oligonucleotides of varying sequences

AU Narayanaswamy, Mathangi; Griffiths, William J.; Howard, Philip W.; Thurston, David E.

CS School of Pharmacy, University of London, London, WCIN 1AX, UK

SO Analytical Biochemistry (2008), 374(1), 173-181

CODEN: ANBCA2; ISSN: 0003-2697

PB Elsevier

DT Journal

LA English

AB The main method of evaluating the DNA interstrand crosslinking ability of cancer chemotherapeutic agents in naked DNA currently involves the electrophoresis of relatively long radiolabeled duplex DNA fragments (typically .apprx.2000 bp) on neutral gels after incubation with the agent of interest. Denaturation by heating is carried out prior to loading, and a neutral gel allows reannealing of crosslinked DNA. To avoid the use of radioactivity we have developed a new method based on ion pair reversed phase liquid chromatog. (RPLC) and mass spectrometry (MS) that allows characterization and quantitation of drug-DNA interstrand crosslinks formed within short oligonucleotide duplexes (i.e., 12 bp). Advantages of this assay include rapid throughput, as compared to electrophoretic methods, and the use of readily available short nonradiolabeled oligonucleotides of any sequence, thereby facilitating investigation of sequence selectivity. A further advantage is that all species separated by the chromatog. process can be pos. identified by MS. Using this new method, we have investigated the rate of DNA crosslinking and sequence selectivity of the interstrand crosslinking agent SJG-136, a pyrrolobenzodiazepine (PBD) dimer currently in phase I clin. trials. The assay was found to be sufficiently sensitive and selective to allow separation of the unbound and drug-bound oligonucleotide species by high-performance liquid chromatog. (HPLC) and to allow pos. identification of these individual species by MS. A further benefit, as compared with electrophoretic methods, is that kinetic information can be obtained and compared for different binding sequences.

IT 232931-57-6, SJG-136

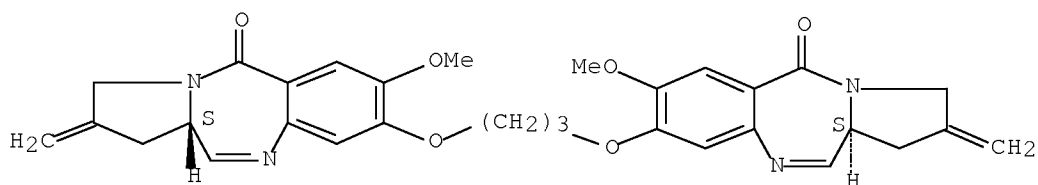
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(assay combining high-performance liquid chromatog. and mass spectrometry to measure DNA interstrand crosslinking efficiency)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



L18 ANSWER 5 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2008:90856 CAPLUS Full-text

DN 148:190128

TI Antagonist antibody for the treatment of cancer

IN Blanc, Veronique; Fromond, Claudia; Parker, Fabienne; Han, Jiawen;  
Tavares, Daniel; Zhang, Chonghui; Li, Min; Zhou, Xiao-Mai; Streuli, Michel

PA Sanofi-Aventis, Germany

SO PCT Int. Appl., 134pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 2008010101	A2	20080124	WO 2007-IB3074	20070713
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
	RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

PRAI EP 2006-291160 A 20060718

AB Antibodies, humanized antibodies, resurfaced antibodies, antibody fragments, derivatized antibodies, and conjugates of same with cytotoxic agents, which specifically bind to, and inhibit A class of Eph receptors, antagonize the effects of growth factors on the growth and survival of tumor cells, and which have minimal agonistic activity or are preferentially devoid of agonist activity are described. Said antibodies and fragments thereof may be used in the treatment of tumors that express elevated levels of A class of Eph receptors, such as breast cancer, colon cancer, lung cancer, ovarian carcinoma, synovial sarcoma and pancreatic cancer, and said derivatized antibodies may be used in the diagnosis and imaging of tumors that express elevated levels of A class of Eph receptors. Also provided are cytotoxic conjugates comprising a cell binding agent and a cytotoxic agent, therapeutic compns. comprising the conjugate, methods for using the conjugates in the inhibition of cell growth and the treatment of disease, and a kit comprising the cytotoxic conjugate are disclosed are all embodiments of the invention. In particular, the cell binding agent is a monoclonal antibody, and epitope-binding fragments thereof, that recognizes and binds the A class of Eph receptors.

IT 877659-86-4D, antibody conjugates 945489-85-0D, antibody conjugates 945489-86-1D, antibody conjugates 945489-88-3D, antibody conjugates 945489-89-4D, antibody conjugates 945489-90-7D, antibody conjugates 945489-91-8D, antibody conjugates 945489-95-2D, antibody conjugates 945490-00-6D, antibody conjugates 945490-04-0D, antibody conjugates 945490-10-8D, antibody conjugates 945490-12-0D, antibody conjugates 945490-23-3D, antibody conjugates 945490-31-3D, antibody conjugates 945490-37-9D, antibody conjugates 945490-40-4D, antibody conjugates 945490-42-6D, antibody conjugates 945490-46-0D, antibody conjugates 945490-54-0D, antibody conjugates 945490-59-5D, antibody conjugates 945490-63-1D, antibody conjugates

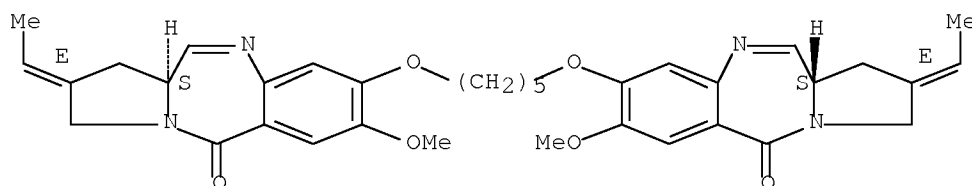
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conjugates 945490-76-6D, antibody conjugates  
945490-80-2D, antibody conjugates 945490-85-7D, antibody  
conjugates 945490-88-0D, antibody conjugates  
1001321-52-3D, antibody conjugates 1001321-53-4D,  
antibody conjugates 1001321-54-5D, antibody conjugates  
1001321-55-6D, antibody conjugates

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(anti-EphA2 receptor antibody plus cytotoxic agent for treatment of  
cancer)

RN 877659-86-4 CAPLUS

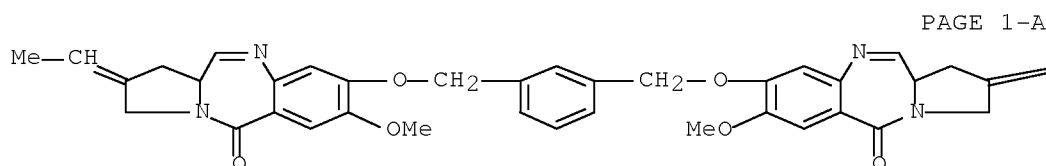
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-  
pentanediylbis(oxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-,  
(2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.



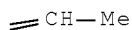
RN 945489-85-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
phenylenebis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-,  
(2E,2'E,11aS,11'aS)- (CA INDEX NAME)



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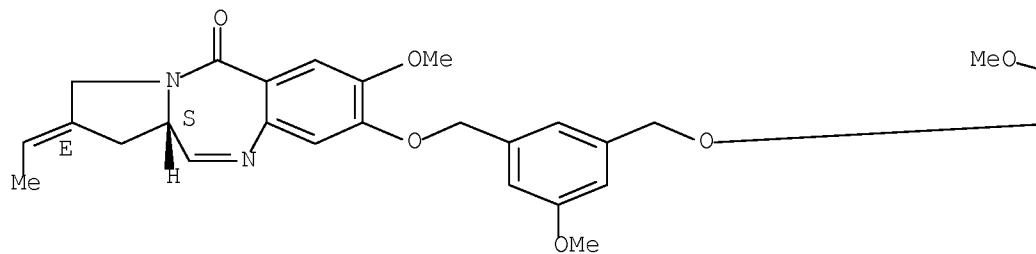


RN 945489-86-1 CAPLUS

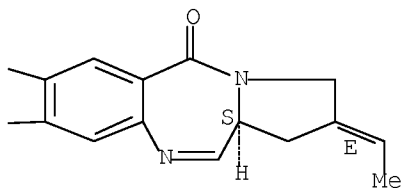
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[(5-methoxy-1,3-  
phenylene)bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-  
methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A

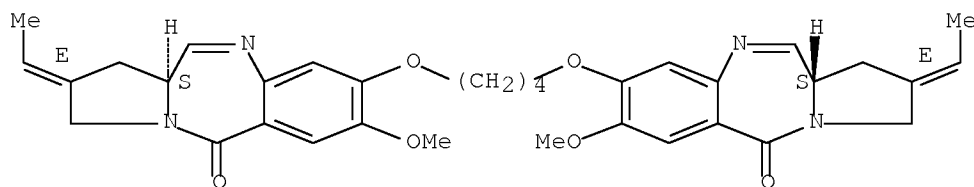


PAGE 1-B



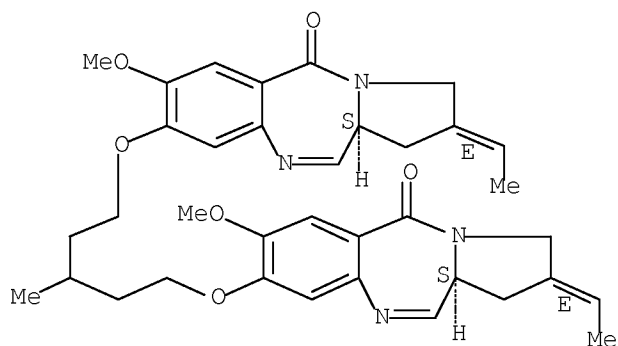
RN 945489-88-3 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[2-ethyldene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as shown.



RN 945489-89-4 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[(3-methyl-1,5-pentanediy1)bis(oxy)]bis[2-ethyldene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

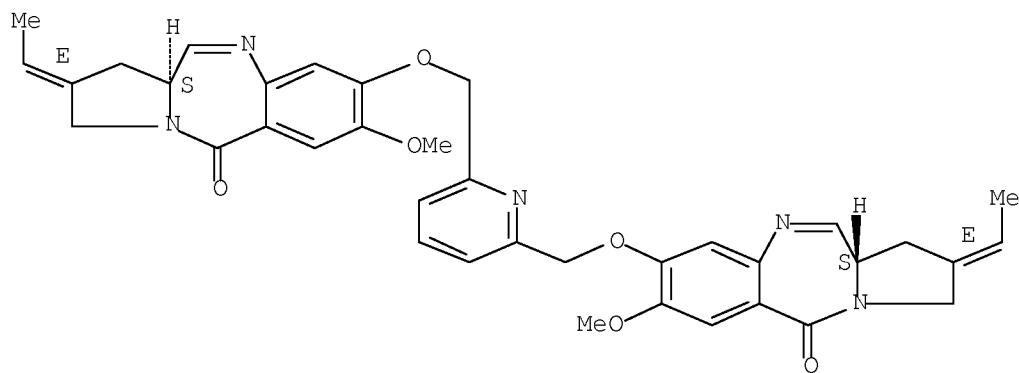
Absolute stereochemistry.  
 Double bond geometry as shown.



RN 945489-90-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[2,6-pyridinediylbis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

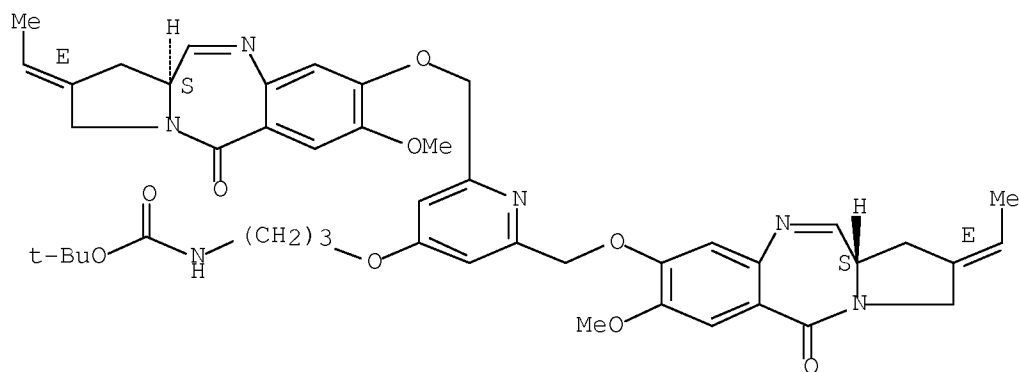
Absolute stereochemistry.  
Double bond geometry as shown.



RN 945489-91-8 CAPLUS

CN Carbamic acid, N-[3-[[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]-4-pyridinyl]oxy]propyl]-, 1,1-dimethylethyl ester (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

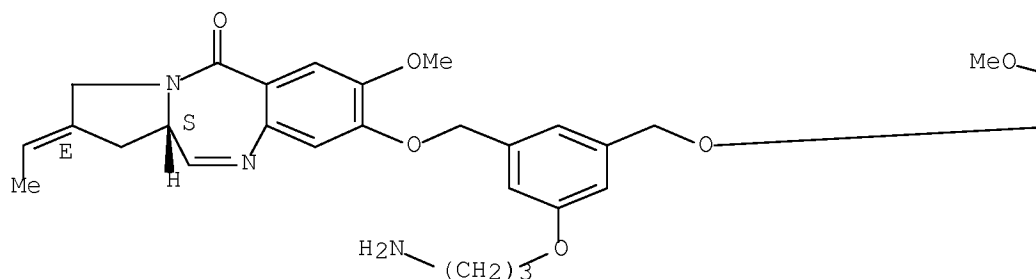


RN 945489-95-2 CAPLUS

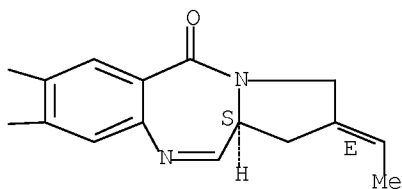
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[5-(3-aminopropoxy)-1,3-phenylene]bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

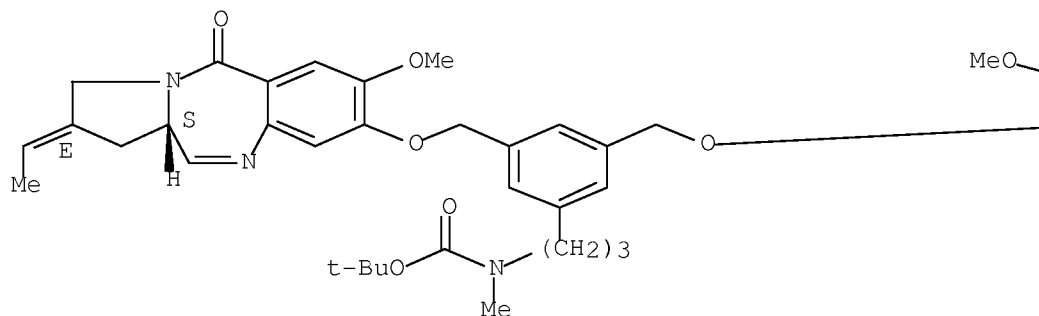


RN 945490-00-6 CAPLUS

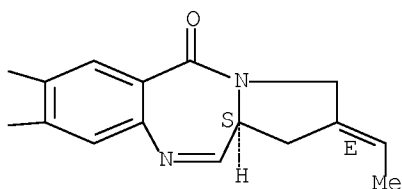
CN Carbamic acid, N-[3-[3,5-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenyl]propyl]-N-methyl-, 1,1-dimethylethyl ester (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A



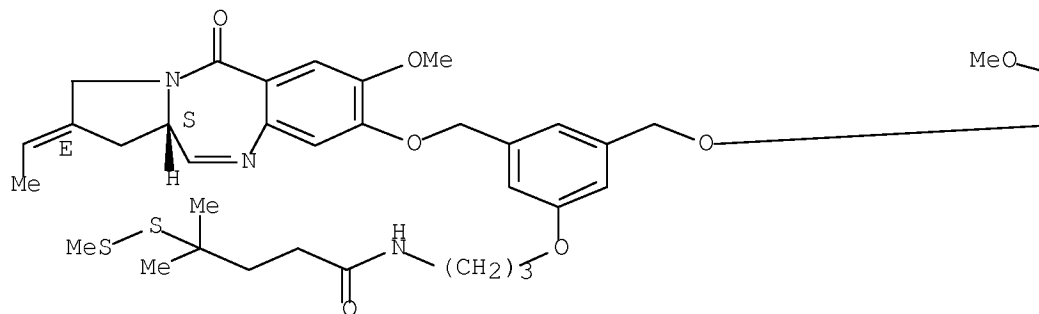
PAGE 1-B

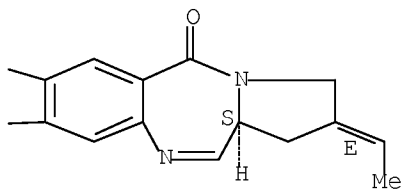


RN 945490-04-0 CAPLUS  
CN Pentanamide, N-[3-[3,5-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenoxy]propyl]-4-methyl-4-(methyldithio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A

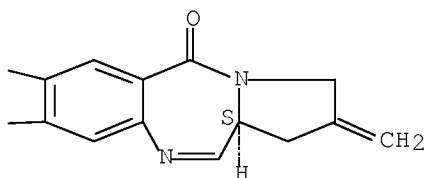
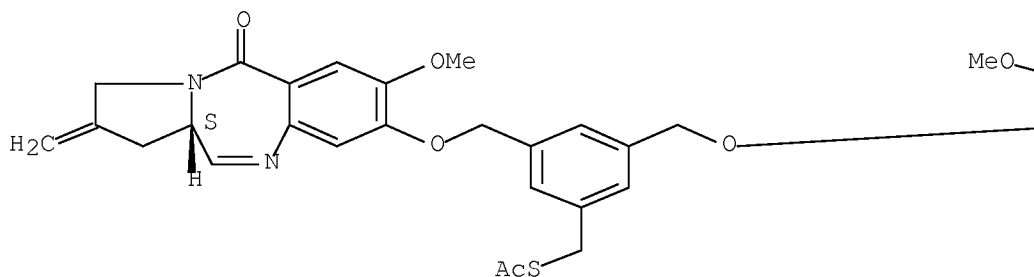




RN 945490-10-8 CAPLUS

CN Ethanethioic acid, S-[[3,5-bis[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy)methyl]phenyl]methyl] ester (CA INDEX NAME)

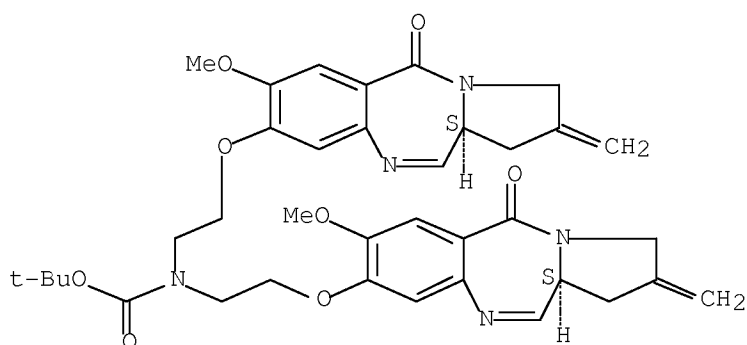
Absolute stereochemistry.



RN 945490-12-0 CAPLUS

CN Carbamic acid, N,N-bis[2-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]ethyl]-, 1,1-dimethylethyl ester (CA INDEX NAME)

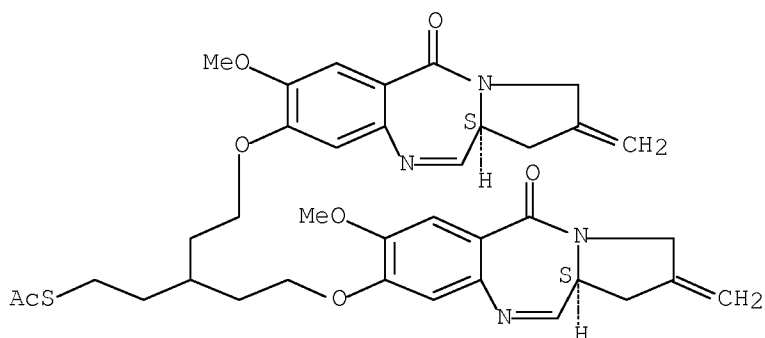
Absolute stereochemistry.



RN 945490-23-3 CAPLUS

CN Ethanethioic acid, S-[5-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-3-[2-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]ethyl]pentyl] ester (CA INDEX NAME)

Absolute stereochemistry.



RN 945490-31-3 CAPLUS

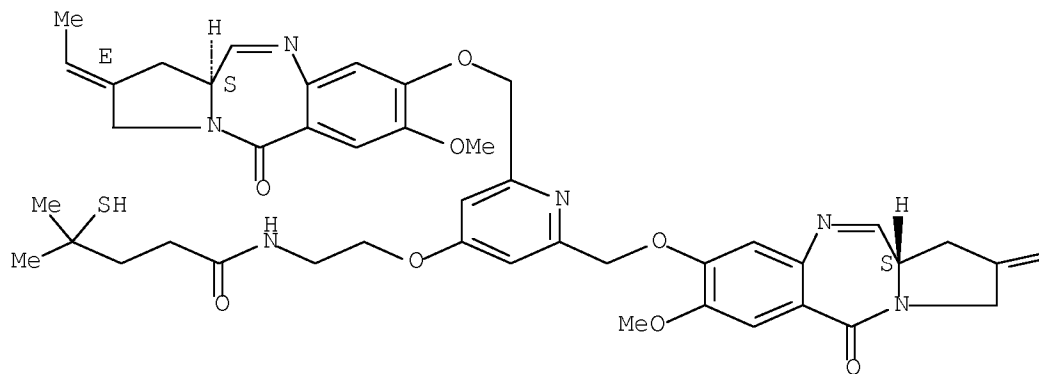
CN Pentanamide, N-[2-[[[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]-4-pyridinyl]oxy]ethyl]-4-mercapto-4-methyl- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.



PAGE 1-A



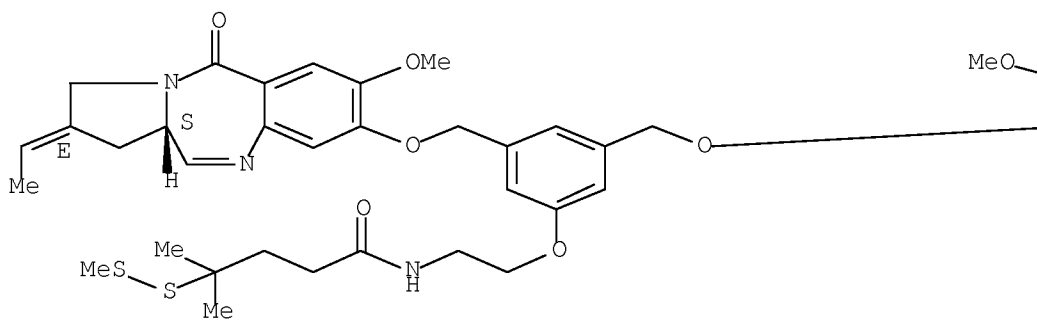
PAGE 1-B

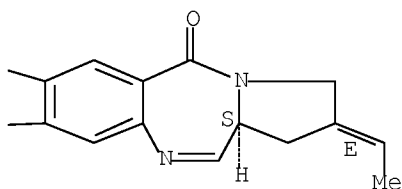


RN 945490-37-9 CAPLUS  
 CN Pentanamide, N-[2-[3,5-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenoxy]ethyl]-4-methyl-4-(methyldithio)- (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as shown.

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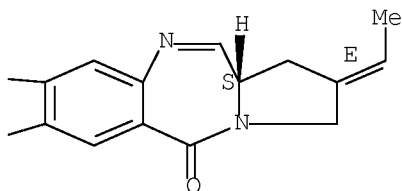
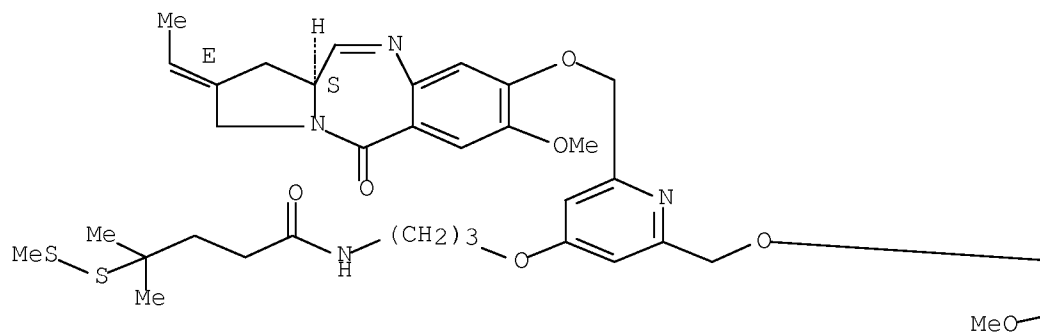




RN 945490-40-4 CAPLUS

CN Pentanamide, N-[3-[[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]-4-pyridinyl]oxy]propyl]-4-methyl-4-(methyldithio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

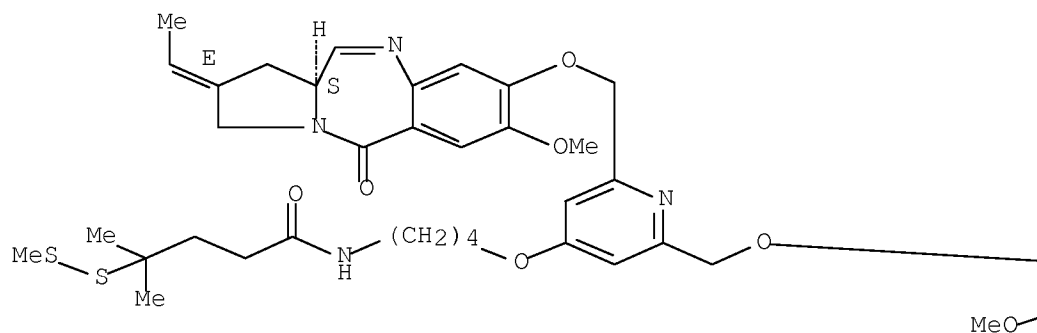


RN 945490-42-6 CAPLUS

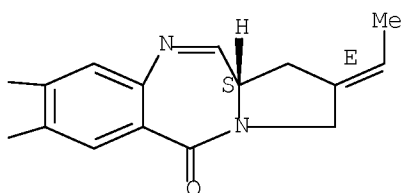
CN Pentanamide, N-[4-[[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]-4-pyridinyl]oxy]butyl]-4-methyl-4-(methylthio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A

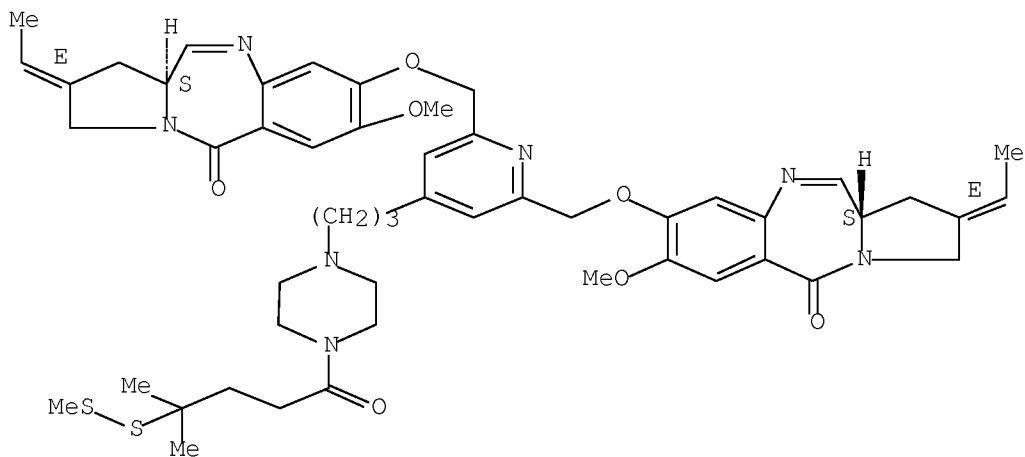


PAGE 1-B



RN 945490-46-0 CAPLUS  
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[4-[3-[4-[4-methyl-4-(methylthio)-1-oxopentyl]-1-piperazinyl]propyl]-2,6-pyridinediyl]bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

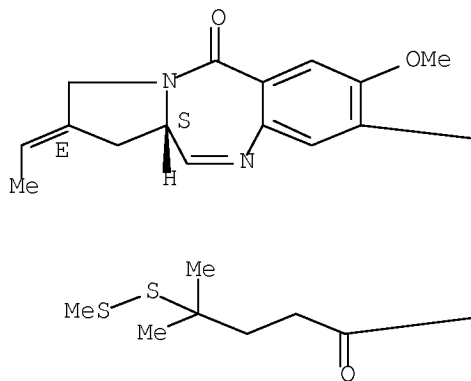


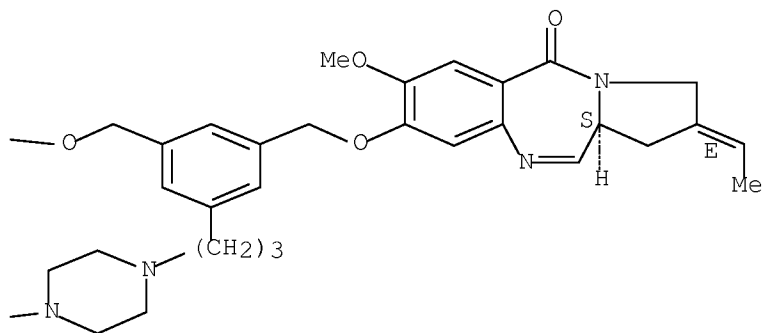
RN 945490-54-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[5-[3-[4-[4-methyl-4-(methyldithio)-1-oxopentyl]-1-piperazinyl]propyl]-1,3-phenylene]bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A

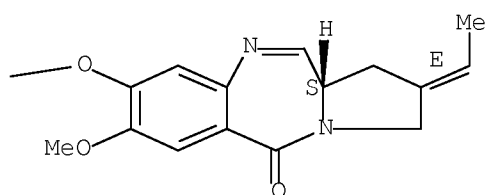
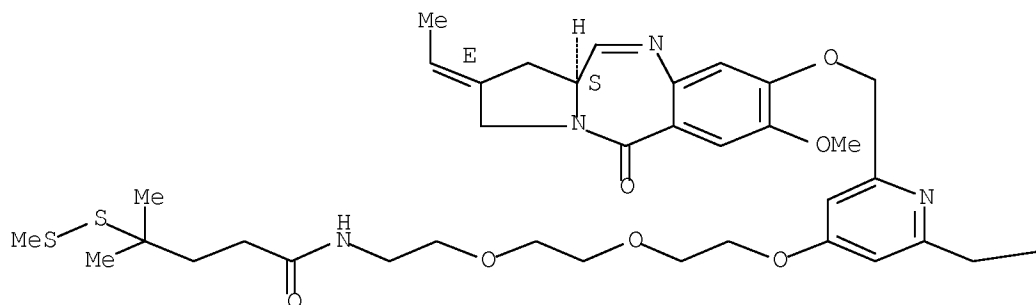




RN 945490-59-5 CAPLUS

CN Pentanamide, N-[2-[2-[2-[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]-4-pyridinyl]oxy]ethoxy]ethoxy]ethyl]-4-methyl-4-(methylthio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

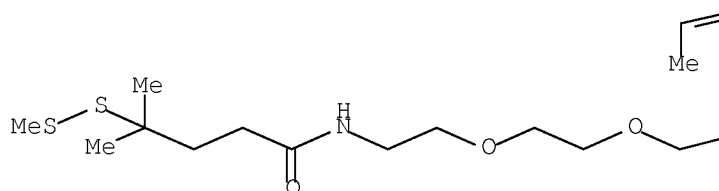


RN 945490-63-1 CAPLUS

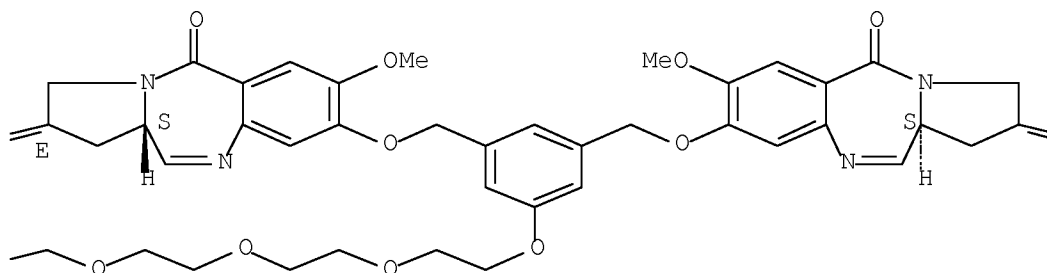
CN Pentanamide, N-[17-[3,5-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenoxy]-3,6,9,12,15-pentaoxaheptadec-1-yl]-4-methyl-4-(methylthio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



PAGE 1-C



RN 945490-67-5 CAPLUS

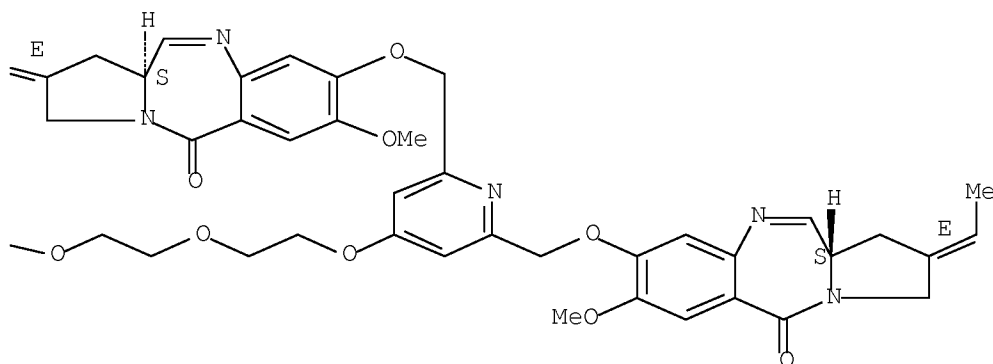
CN Pentanamide, N-[2-[2-[2-[3,5-bis[[[(2E,11aS)-2-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-

Absolute stereochemistry.  
Double bond geometry as shown.

COc1cc2c(c1)c(=O)n3c2cnc3C(=C)C[C@H]4SCC(C4)C(=O)NCCOCCOCCOCCOc5ccc(OC)cc5COc6ccc(OC)cc6

Absolute stereochemistry.  
Double bond geometry as shown.

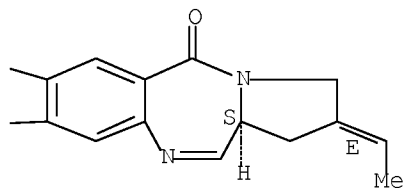
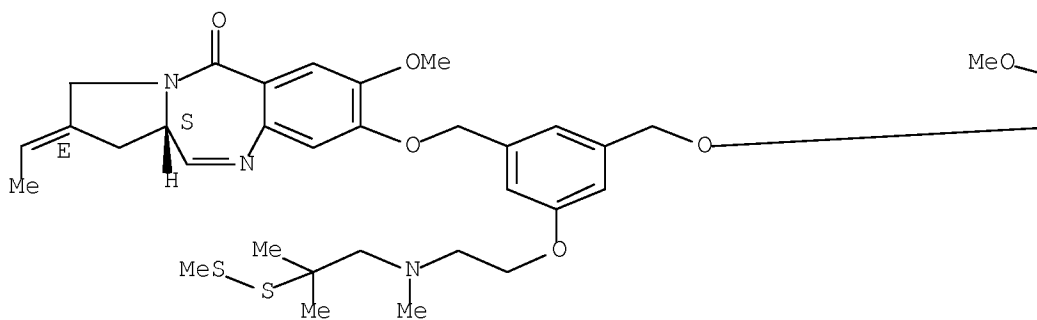
CC(C)(CS)CCC(=O)NCCOCCOCCOCCOCC=C



RN 945490-76-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[5-[2-[methyl[2-methyl-2-(methyldithio)propyl]amino]ethoxy]-1,3-phenylene]bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.



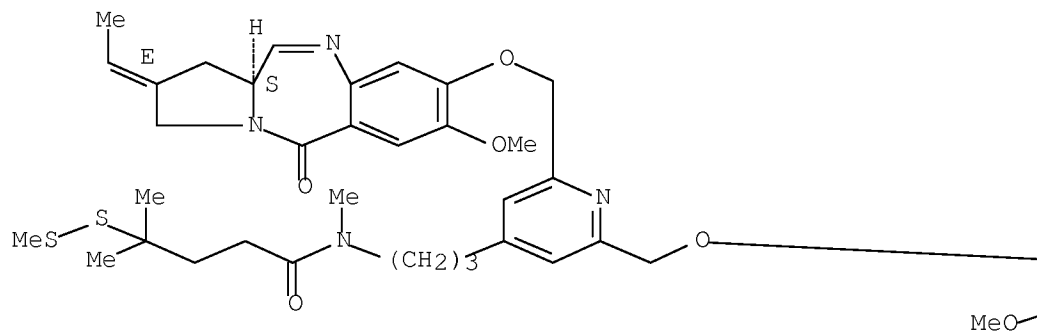


RN 945490-80-2 CAPLUS

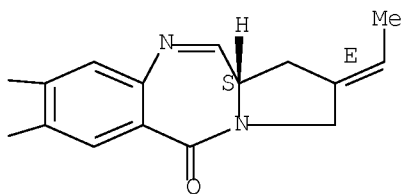
CN Pentanamide, N-[3-[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy)methyl]-4-pyridinyl]propyl]-N,4-dimethyl-4-(methyldithio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A



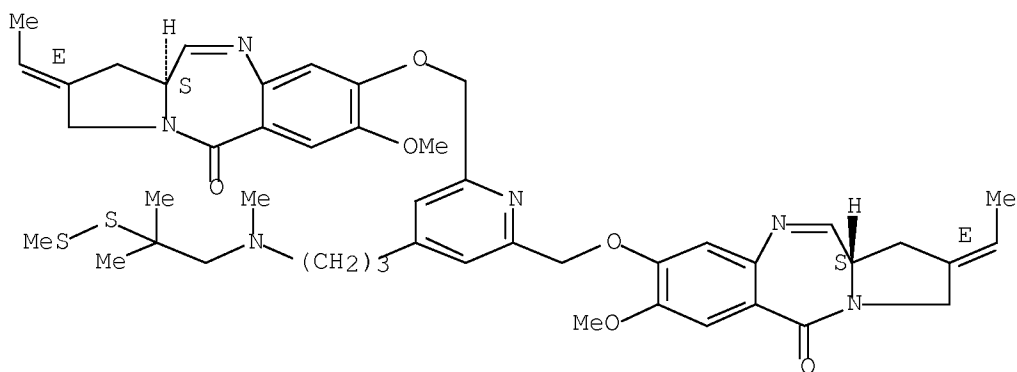
PAGE 1-B



RN 945490-85-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[4-[3-[methyl[2-methyl-2-(methyldithio)propyl]amino]propyl]-2,6-pyridinediyl]bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

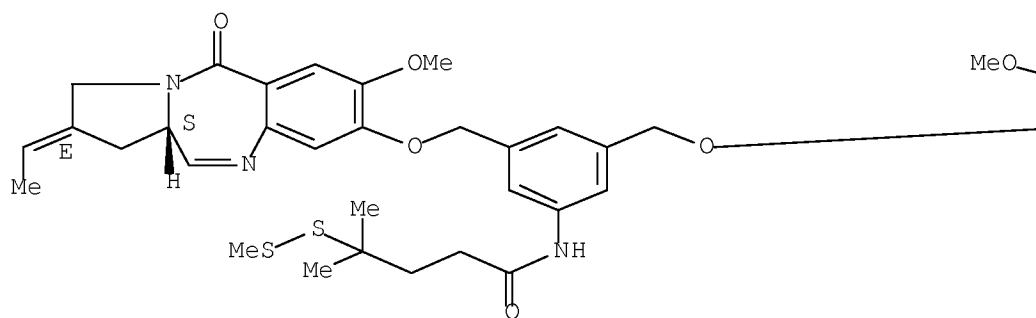


RN 945490-88-0 CAPLUS

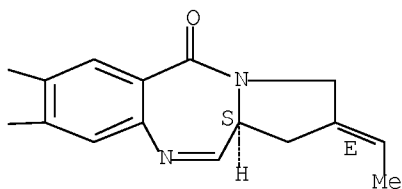
CN Pentanamide, N-[3,5-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenyl]-4-methyl-4-(methylthio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

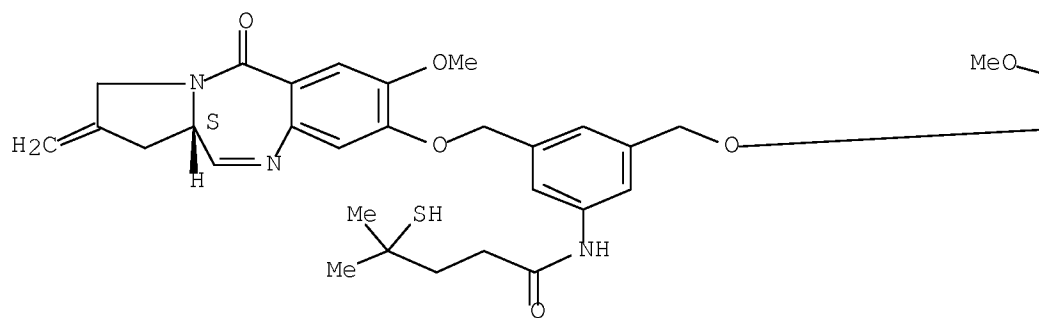


RN 1001321-52-3 CAPLUS

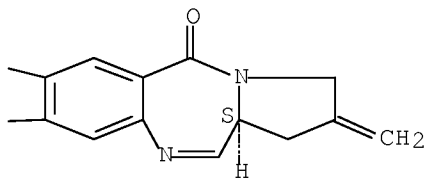
CN Pentanamide, N-[3,5-bis[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenyl]-4-mercapto-4-methyl- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



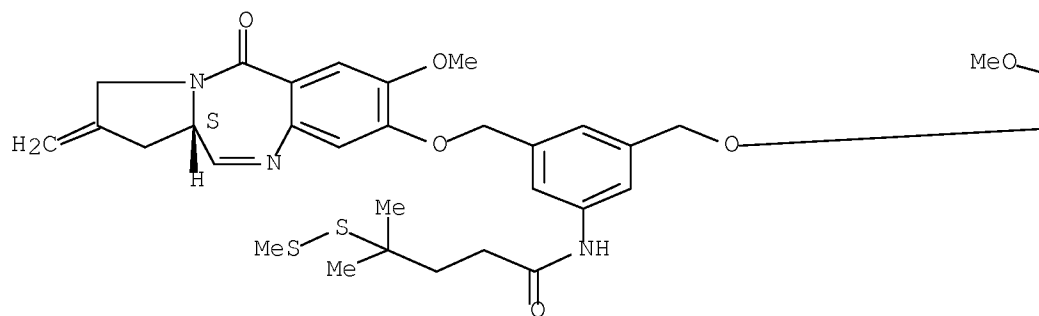
PAGE 1-B

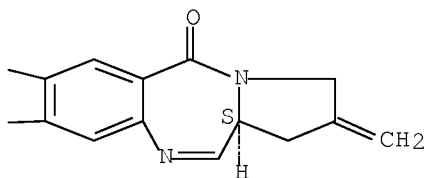


RN 1001321-53-4 CAPLUS  
CN Pentanamide, N-[3,5-bis[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenyl]-4-methyl-4-(methylthio)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

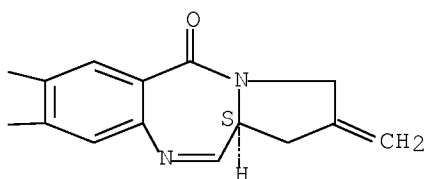
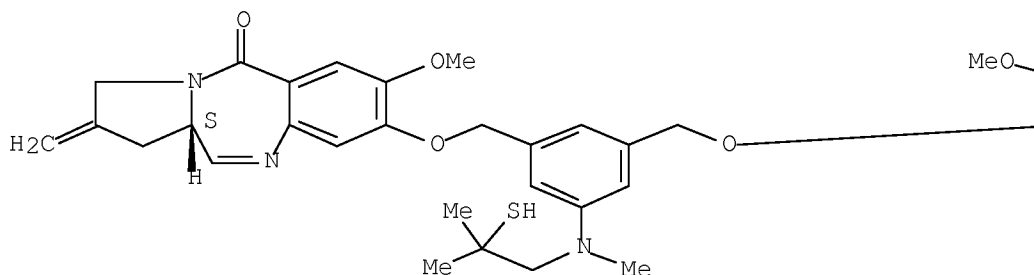




RN 1001321-54-5 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[5-[(2-mercapto-2-methylpropyl)methylamino]-1,3-phenylene]bis(methyleneoxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.

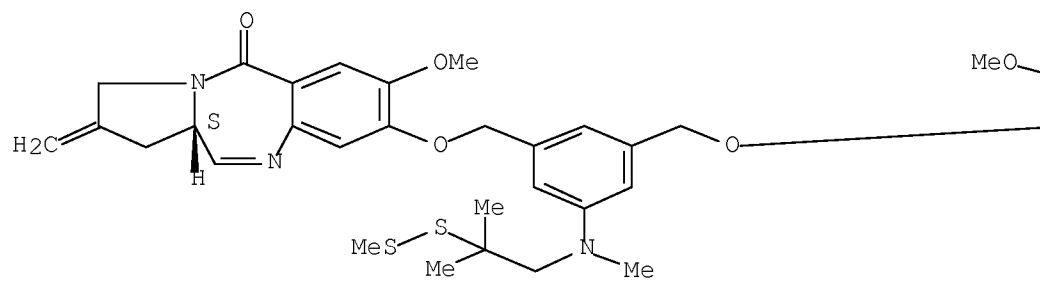


RN 1001321-55-6 CAPLUS

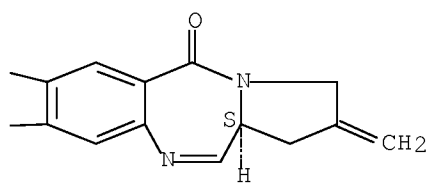
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[5-[methyl[2-methyl-2-(methylthio)propyl]amino]-1,3-phenylene]bis(methyleneoxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



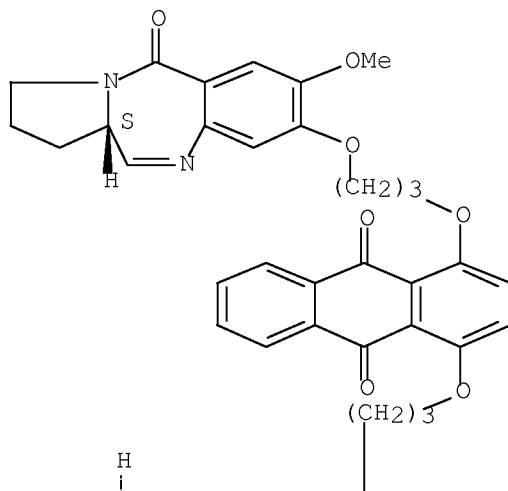
PAGE 1-B

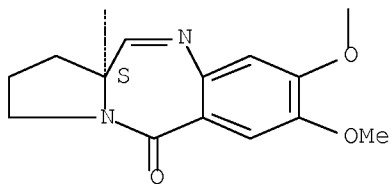


L18 ANSWER 6 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2007:1111757 CAPLUS Full-text  
 DN 147:514384  
 TI Synthesis, DNA binding, and cytotoxicity studies of pyrrolo[2,1-c][1,4]benzodiazepine-anthraquinone conjugates  
 AU Kamal, Ahmed; Ramu, R.; Tekumalla, Venkatesh; Khanna, G. B. Ramesh; Barkume, Madan S.; Juvekar, Aarti S.; Zingde, Surekha M.  
 CS Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad, 500 007, India  
 SO Bioorganic & Medicinal Chemistry (2007), 15(22), 6868-6875  
 CODEN: BMECEP; ISSN: 0968-0896  
 PB Elsevier Ltd.  
 DT Journal  
 LA English  
 OS CASREACT 147:514384  
 AB A series of pyrrolo[2,1-c][1,4]benzodiazepine-anthraquinone conjugates have been prepared and evaluated for their DNA binding ability as well as anticancer activity. Some of these mols. have shown significant anticancer activity in a number of cancer cell lines.  
 IT 946856-66-2P 946856-67-3P 946856-68-4P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (pyrrolo benzodiazepine anthraquinones as DNA-binding anticancer agents)  
 RN 946856-66-2 CAPLUS  
 CN 9,10-Anthracenedione, 1,4-bis[3-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

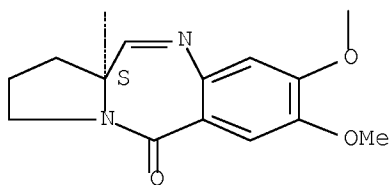
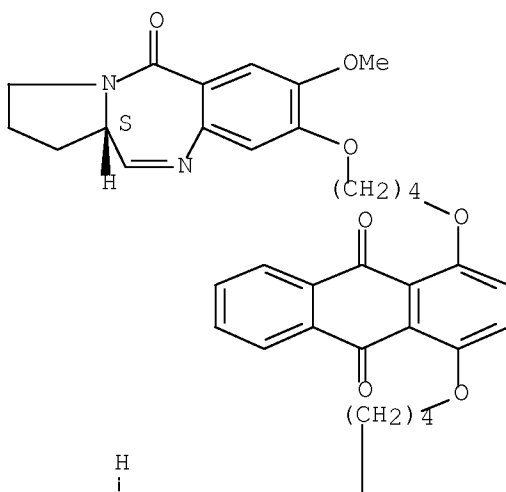




RN 946856-67-3 CAPLUS

CN 9,10-Anthracenedione, 1,4-bis[4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]- (CA INDEX NAME)

Absolute stereochemistry.

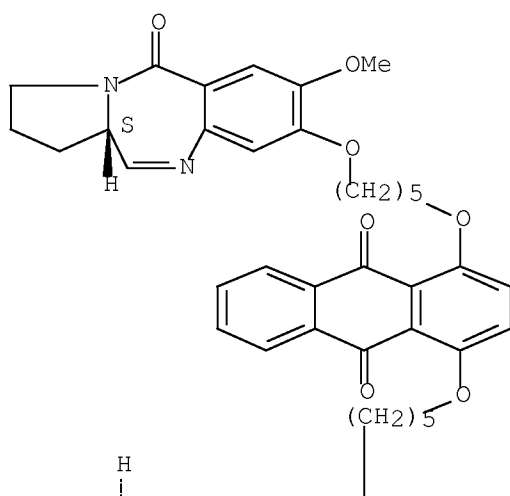


RN 946856-68-4 CAPLUS

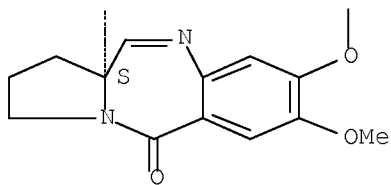
CN 9,10-Anthracenedione, 1,4-bis[[5-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



L18 ANSWER 7 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2007:1061083 CAPLUS Full-text

DN 147:386027

TI Preparation of bis-2-difluoro-pyrrolo[2,1-c][1,4]benzodiazepine dimers via condensation, reduction, and cyclization reactions and their binding affinity with calf thymus DNA

IN Kamal, Ahmed; Reddy, Depatla Rajasekhar; Rajender, .

PA Council of Scientific and Industrial Research, India

SO PCT Int. Appl., 22pp.

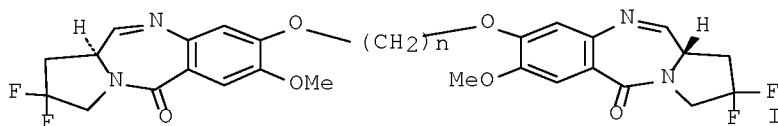
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2007105045	A1	20070920	WO 2007-IB448	20070226
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
	RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	US 20070249828	A1	20071025	US 2007-715592	20070307
PRAI	IN 2006-DE669	A	20060310		
OS	CASREACT 147:386027; MARPAT 147:386027				
GI					



AB The present invention provides a process for the preparation of bis-2-difluoro-pyrrolo[2,1-c][1,4]benzodiazepine dimers I, wherein n is 3 to 10 were prepared and showed biding affinity with calf thymus DNA at a molar ratio of 1:5 in aqueous sodium phosphate buffer at pH of about 7.00. Thus, bis-2-difluoro-pyrrolo[2,1-c][1,4]benzodiazepine I (n = 3) was prepared by condensation of (2S)-N-[4-hydroxy-5-methoxy-2-nitrobenzoyl]-4,4-difluoropyrrolidine-2-carboxaldehyde di-Et thioacetal with 1,3-dibromopropane, followed by the nitro group reduction to amino group using SnCl2.2H2O and reductive cyclization using HgCl2/CaCO3.

IT 950191-26-1P 950191-27-2P 950191-28-3P

RL: BSU (Biological study, unclassified); SPN (Synthetic preparation);

BIOL (Biological study); PREP (Preparation)

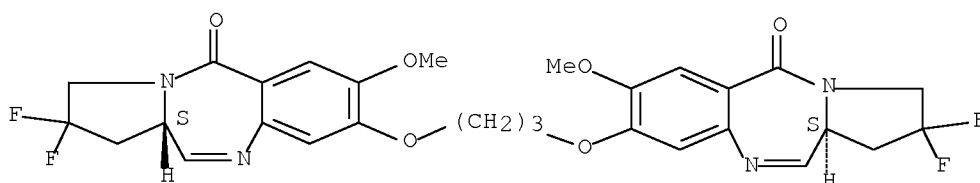
(preparation of bis-2-difluoro-pyrrolo[2,1-c][1,4]benzodiazepine dimers via condensation, reduction, and cyclization reactions and their biding affinity with calf thymus DNA)

RN 950191-26-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-

propanediylbis(oxy)]bis[2,2-difluoro-1,2,3,11a-tetrahydro-7-methoxy-,  
(11aS,11'aS)- (CA INDEX NAME)

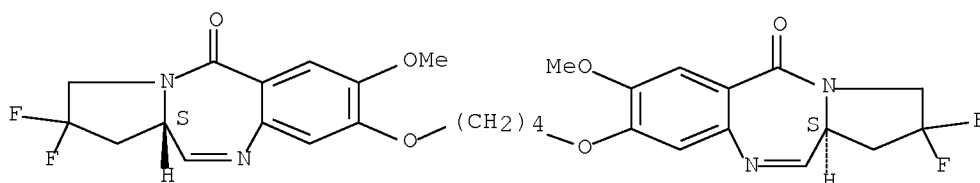
Absolute stereochemistry.



RN 950191-27-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[2,2-difluoro-1,2,3,11a-tetrahydro-7-methoxy-,  
(11aS,11'aS)- (CA INDEX NAME)

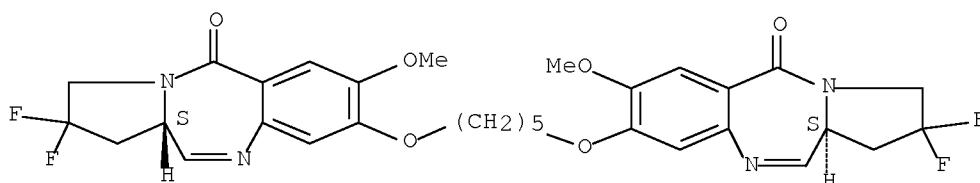
Absolute stereochemistry.



RN 950191-28-3 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediybis(oxy)]bis[2,2-difluoro-1,2,3,11a-tetrahydro-7-methoxy-,  
(11aS,11'aS)- (CA INDEX NAME)

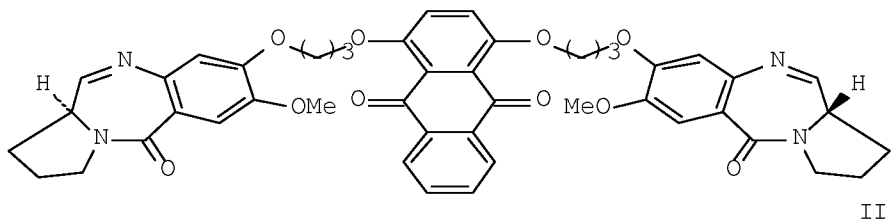
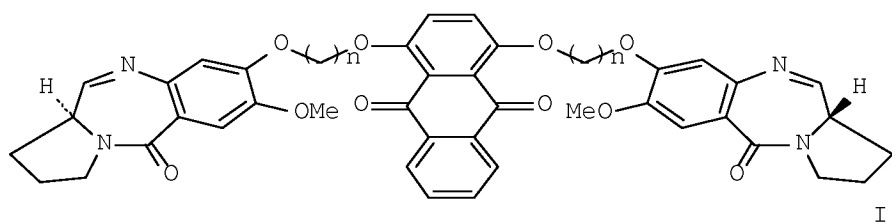
Absolute stereochemistry.



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 8 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2007:934154 CAPLUS Full-text  
 DN 147:301206  
 TI Preparation of anthraquinone derivatives as antitumor agents  
 IN Ahmed, Kamal; Rondla, Ramu; Gollapalli, Bhasker Ramesh Khanna  
 PA Council of Scientific and Industrial Research, India  
 SO PCT Int. Appl., 27pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2007093873	A1	20070823	WO 2007-IB320	20070212
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
	RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	US 20070259858	A1	20071108	US 2007-705660	20070212
PRAI	IN 2006-DE383	A	20060213		
OS	CASREACT 147:301206				
GI					



AB The title compds. with general formula I [wherein n = 3-5] were prepared as antitumor agents. For example, 1,4-dihydroxyanthraquinone was reacted with 1,3-dibromopropane for 1,4-bis(3-bromopropoxy)anthracene-9,10- dione, which was then reacted with (2S)-2-[bis(ethylthio)methyl]-1-(4- hydroxy-5-methoxy-2-nitrobenzoyl)pyrrolidine to obtain an intermediate. The intermediate obtained

above was reduced with tin chloride and then treated with mercuric chloride in presence of calcium carbonate to give II as a final product. II exhibited in vitro anticancer activity with IC50 values of 0.5  $\mu$ M and 0.6  $\mu$ M against ZR-75-1 and PC3 human cancer cell lines, resp.

IT 946856-66-2P 946856-67-3P 946856-68-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

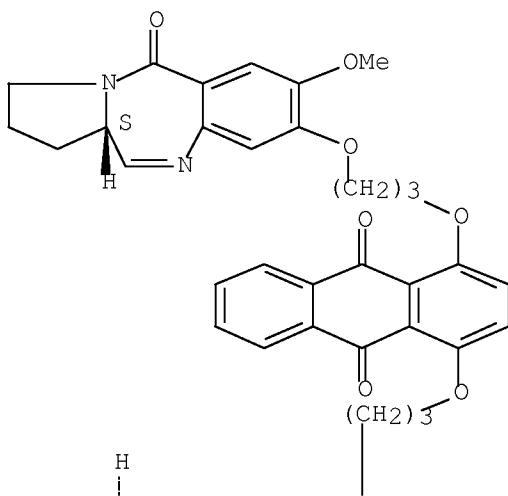
(drug candidate; preparation of anthraquinone derivs. as antitumor agents)

RN 946856-66-2 CAPLUS

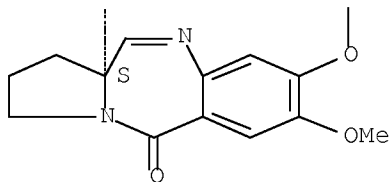
CN 9,10-Anthracenedione, 1,4-bis[3-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

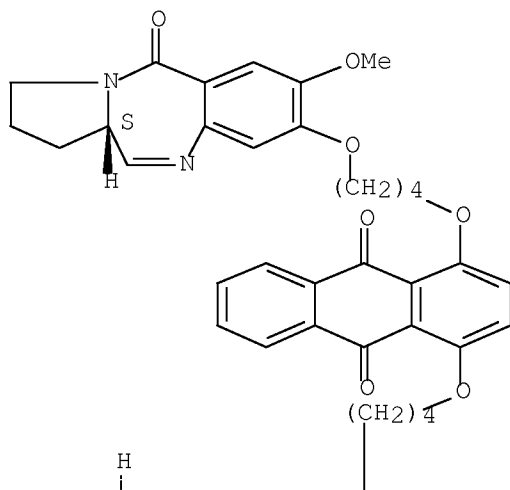


RN 946856-67-3 CAPLUS

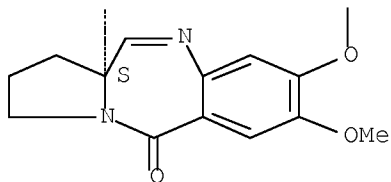
CN 9,10-Anthracenedione, 1,4-bis[4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



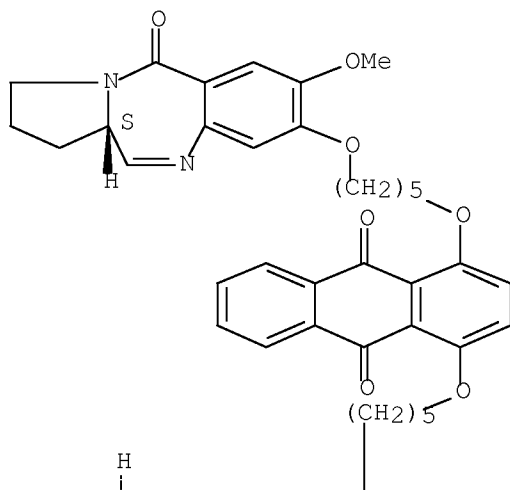
PAGE 2-A



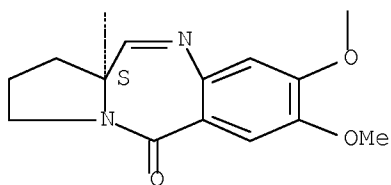
RN 946856-68-4 CAPLUS  
CN 9,10-Anthracenedione, 1,4-bis[[5-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

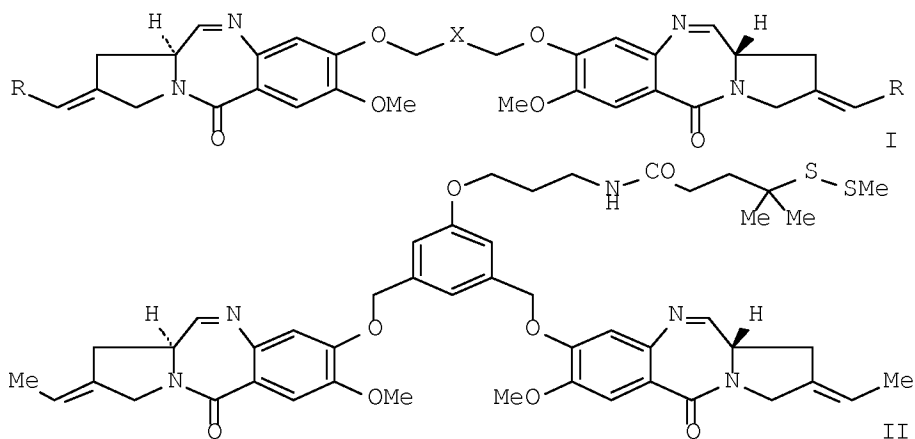


RE.CNT 2

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 9 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2007:838241 CAPLUS Full-text  
 DN 147:234915  
 TI Cytotoxic agents comprising new tomaymycin derivatives and their  
 therapeutic use  
 IN Gauzy, Laurence; Zhao, Robert; Deng, Yonghong; Li, Wei; Bouchard, Herve;  
 Chari, Ravi V. J.; Commercon, Alain  
 PA Sanofi-Aventis, Fr.  
 SO PCT Int. Appl., 173pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2007085930	A1	20070802	WO 2007-IB142	20070122
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM EP 1813614 A1 20070801 EP 2006-290154 20060125 R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU PRAI EP 2006-290154 A 20060125 OS MARPAT 147:234915 GI				



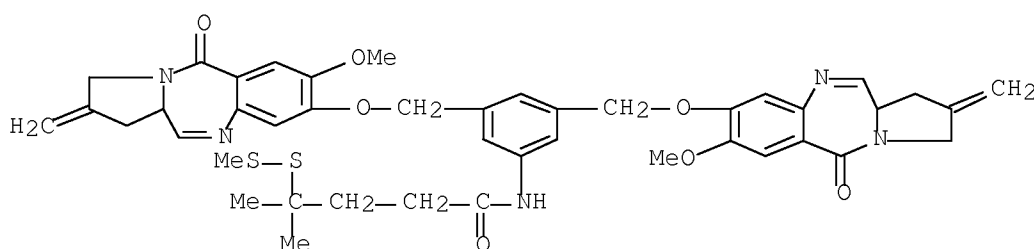
AB Tomaymycin derivs., such as I [R = H, Me; X = alkylene, phenylene, heteroarylene, such as pyridin-2,6-diyl, with or without a heteroalkylene linking group suitable for binding with an antibody], were prepared for therapeutic use as cytotoxic anticancer agents. Thus, tomaymycin derivative II was prepared via a multistep synthetic sequence starting from per-tomaymycin, N-methyl-N-tert-butoxycarbonylpropargylamine, 3,5-bis(methoxycarbonyl)phenyl trifluoromethanesulfonate, and 4-methyl-4-(methyldithio)pentanoic acid. Conjugates of some of the prepared tomaymycin derivs. with antibodies, such as huC242 and huB4, were prepared, and the tomaymycin derivs. and antibody conjugates were tested in vitro for antitumor cytotoxicity against A549, KB, and MCF7 cancer cells.

IT 945489-81-6P 945489-82-7P 945489-83-8P  
945490-32-4P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation of tomaymycin derivs. for therapeutic use as antitumor agents)

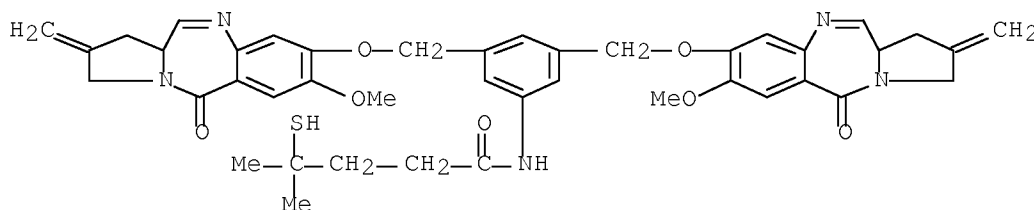
RN 945489-81-6 CAPLUS

CN Pentanamide, N-[3,5-bis[[[(2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl)oxy]methyl]phenyl]-4-methyl-4-(methyldithio)- (CA INDEX NAME)



RN 945489-82-7 CAPLUS

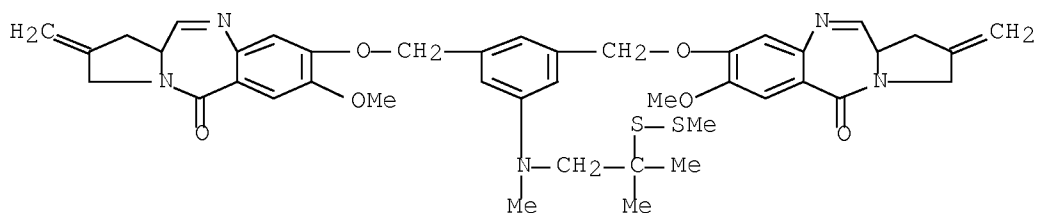
CN Pentanamide, N-[3,5-bis[[[(2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl)oxy]methyl]phenyl]-4-mercapto-4-methyl- (CA INDEX NAME)



RN 945489-83-8 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[5-[methyl[2-methyl-2-(methyldithio)propyl]amino]-1,3-phenylene]bis(methyleneoxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene- (CA INDEX NAME)



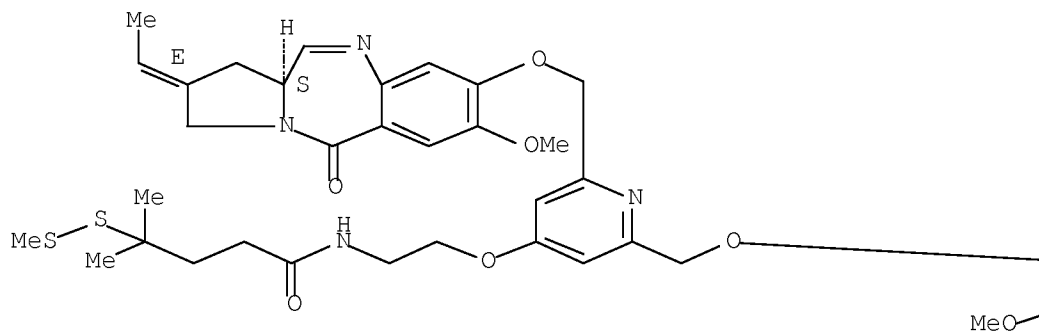


RN 945490-32-4 CAPLUS

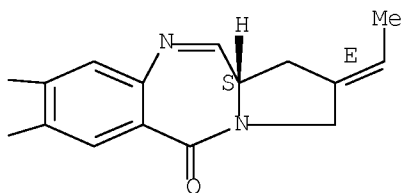
CN Pentanamide, N-[2-[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]-4-pyridinyl]oxy]ethyl]-4-methyl-4-(methylthio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

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IT 877659-86-4P 945489-84-9P 945489-85-0P  
945489-86-1P 945489-88-3P 945489-89-4P

945489-90-7P 945489-91-8P 945489-95-2P  
 945490-00-6P 945490-04-0P 945490-10-8P  
 945490-12-0P 945490-23-3P 945490-31-3P  
 945490-37-9P 945490-40-4P 945490-42-6P  
 945490-46-0P 945490-54-0P 945490-59-5P  
 945490-63-1P 945490-67-5P 945490-71-1P  
 945490-76-6P 945490-80-2P 945490-85-7P  
 945490-88-0P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
 (Uses)

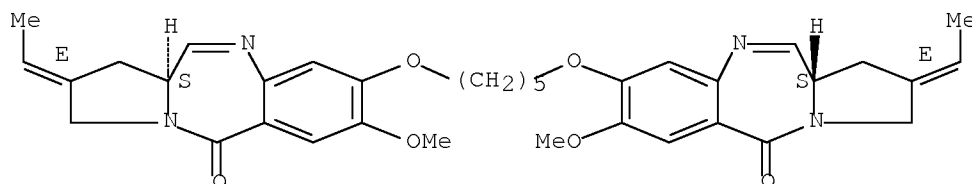
(preparation of tomaymycin derivs. for therapeutic use as antitumor agents)

RN 877659-86-4 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-  
 pentanediylbis(oxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-,  
 (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

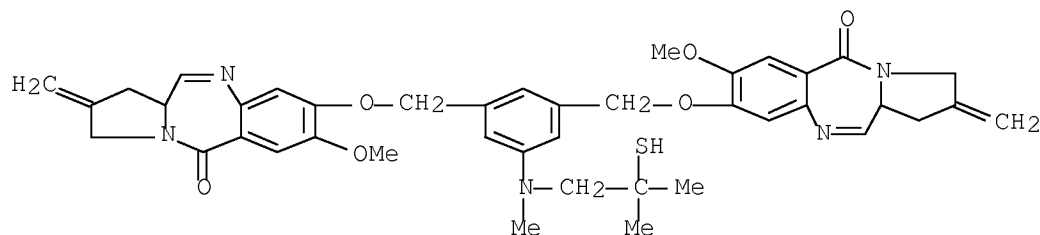
Absolute stereochemistry.

Double bond geometry as shown.



RN 945489-84-9 CAPLUS

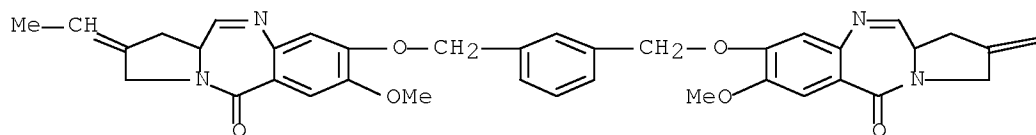
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[5-[(2-mercapto-2-  
 methylpropyl)methylamino]-1,3-phenylene]bis(methyleneoxy)]bis[1,2,3,11a-  
 tetrahydro-7-methoxy-2-methylene- (CA INDEX NAME)



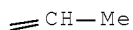
RN 945489-85-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
 phenylenebis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-  
 , (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

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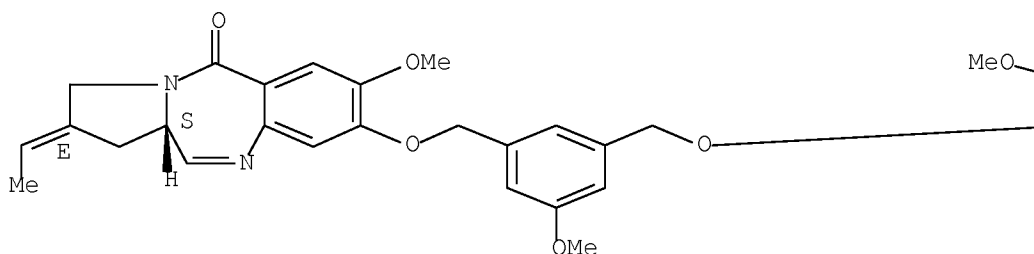


RN 945489-86-1 CAPLUS

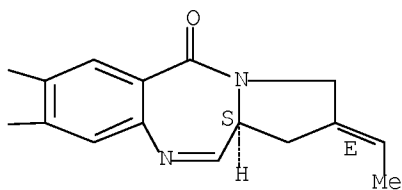
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[(5-methoxy-1,3-phenylene)bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A



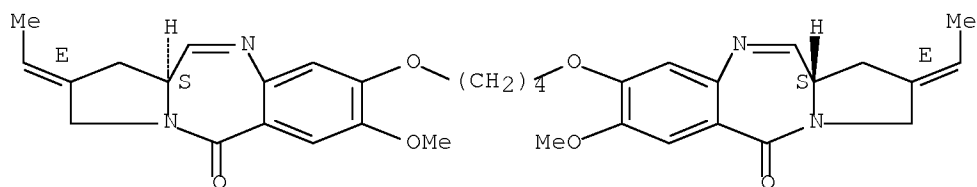
PAGE 1-B



RN 945489-88-3 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

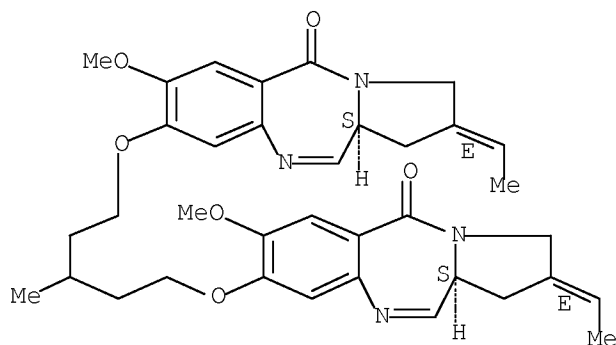
Absolute stereochemistry.  
Double bond geometry as shown.



RN 945489-89-4 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[(3-methyl-1,5-pentanediy1)bis(oxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

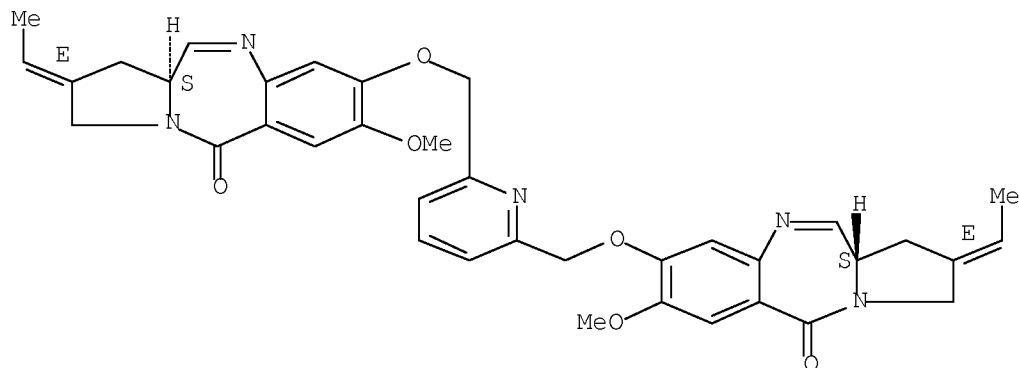
Absolute stereochemistry.  
Double bond geometry as shown.



RN 945489-90-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[2,6-pyridinediylbis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

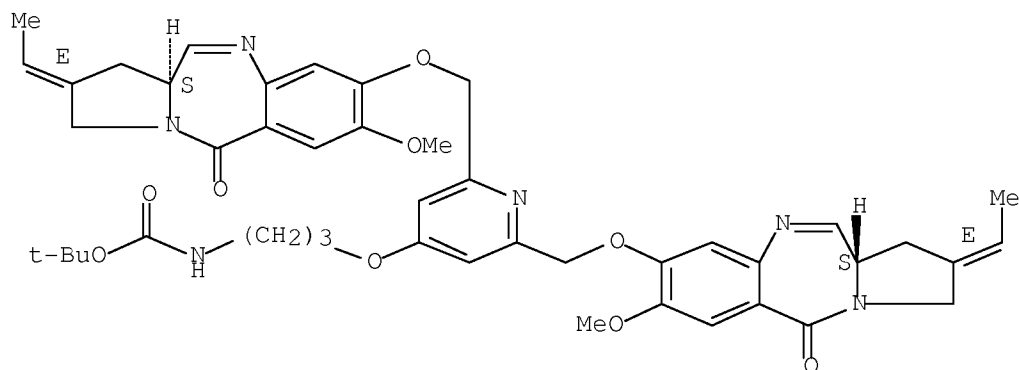
Absolute stereochemistry.  
Double bond geometry as shown.



RN 945489-91-8 CAPLUS

CN Carbamic acid, N-[3-[[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy)methyl]-4-pyridinyl]oxy]propyl]-, 1,1-dimethylethyl ester (CA INDEX NAME)

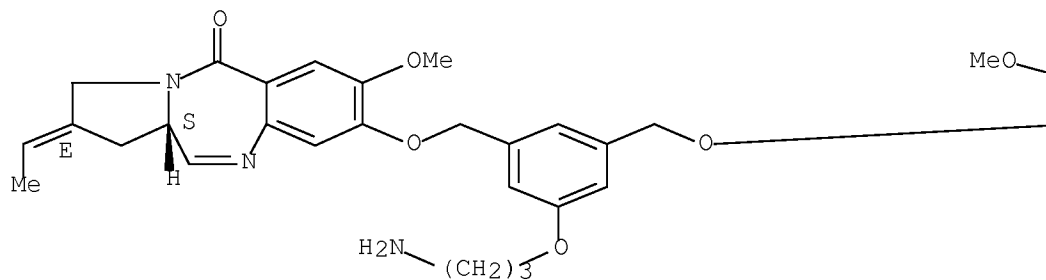
Absolute stereochemistry.  
Double bond geometry as shown.



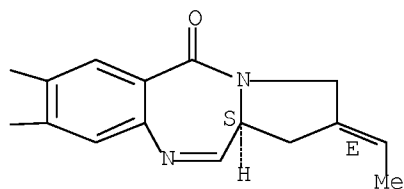
RN 945489-95-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[5-(3-aminopropoxy)-1,3-phenylene]bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.



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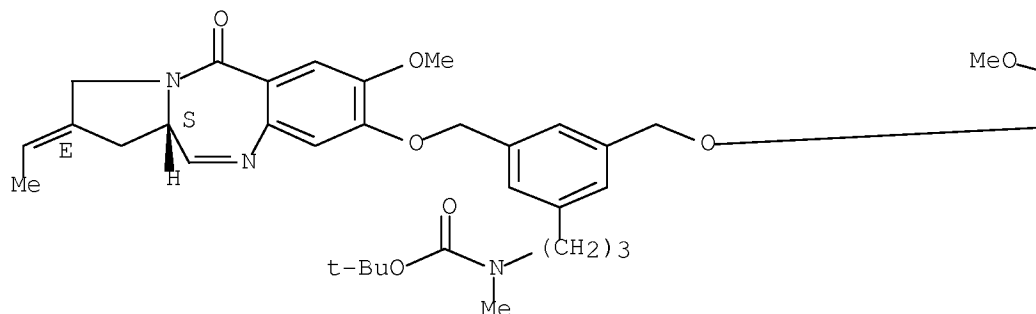
PAGE 1-B

RN 945490-00-6 CAPLUS

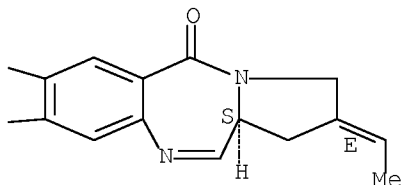
CN Carbamic acid, N-[3-[3,5-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenyl]propyl]-N-methyl-, 1,1-dimethylethyl ester (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

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PAGE 1-B

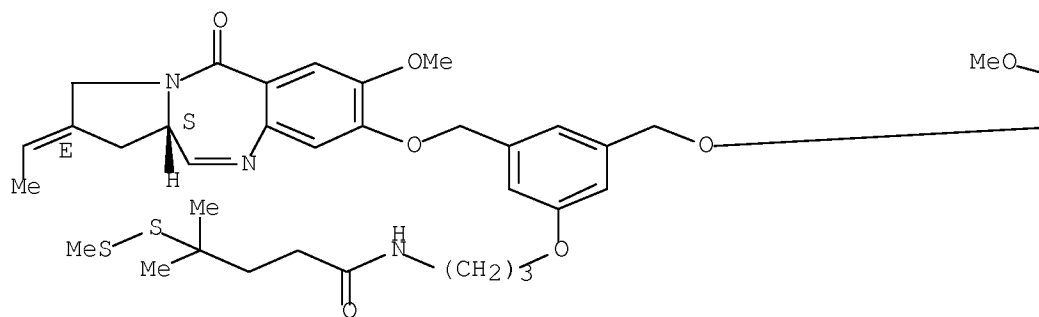


RN 945490-04-0 CAPLUS

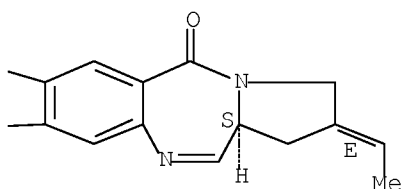
CN Pentanamide, N-[3-[3,5-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenoxy]propyl]-4-methyl-4-(methyldithio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

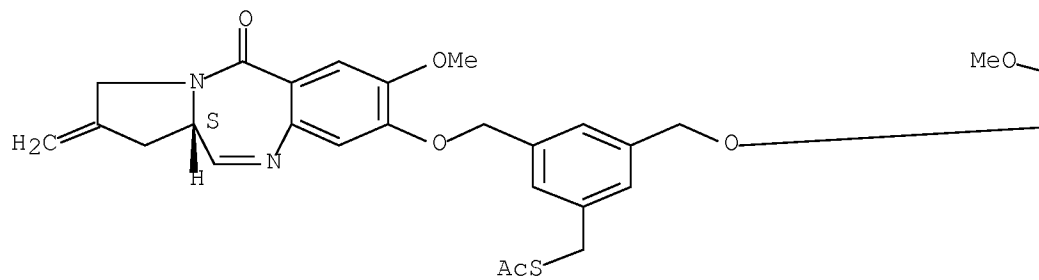


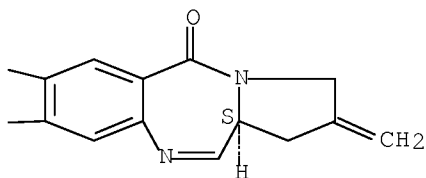
RN 945490-10-8 CAPLUS

CN Ethanethioic acid, S-[[[3,5-bis[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenyl]methyl] ester (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

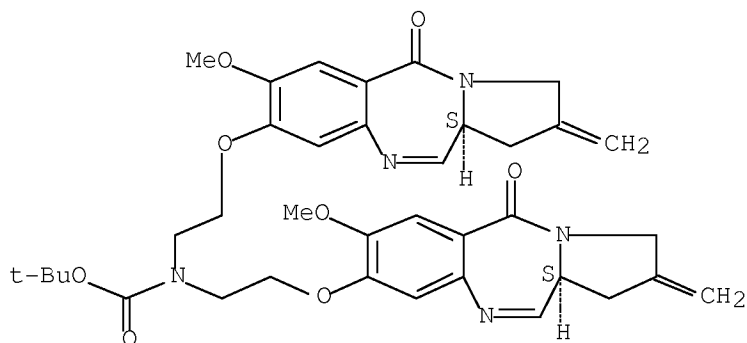




RN 945490-12-0 CAPLUS

CN Carbamic acid, N,N-bis[2-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]ethyl]-, 1,1-dimethylethyl ester (CA INDEX NAME)

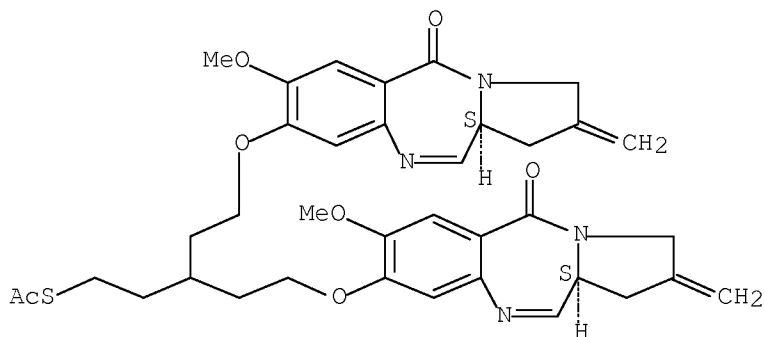
Absolute stereochemistry.



RN 945490-23-3 CAPLUS

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Absolute stereochemistry.



RN 945490-31-3 CAPLUS

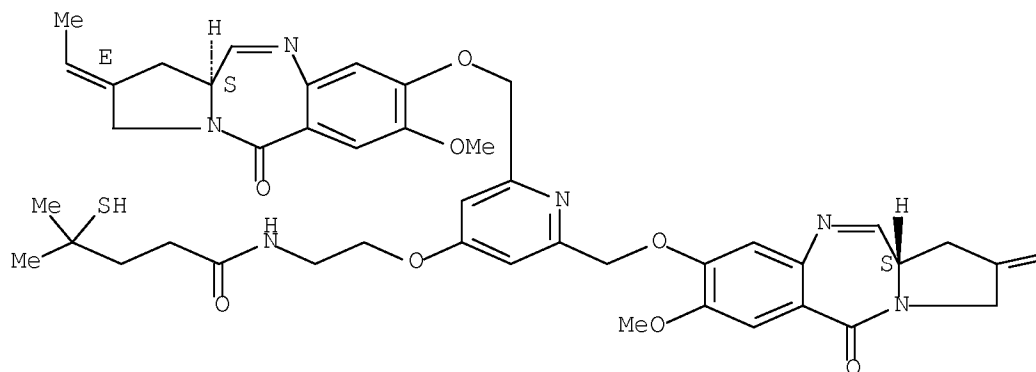
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Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A



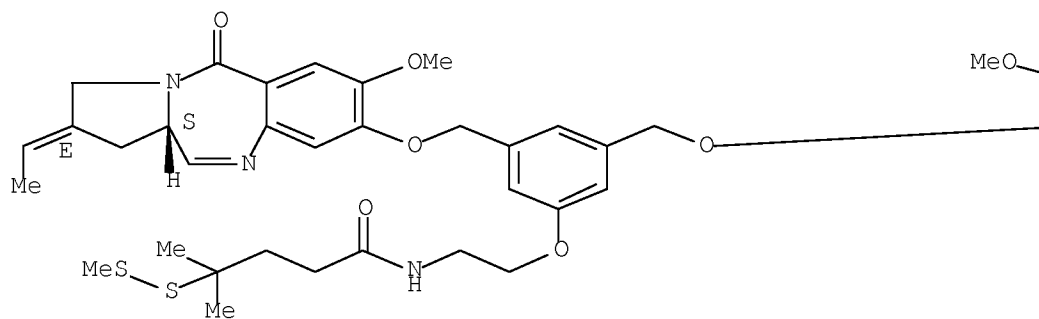
PAGE 1-B



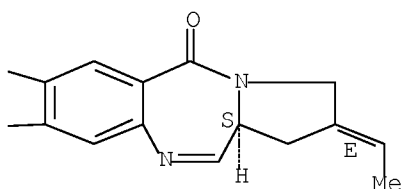
RN 945490-37-9 CAPLUS  
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Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A



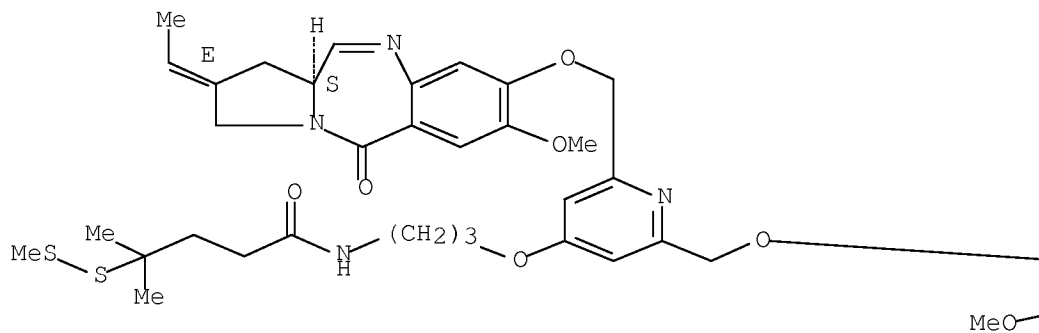
PAGE 1-B

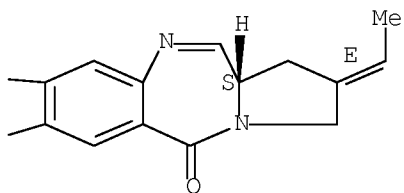


RN 945490-40-4 CAPLUS  
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Absolute stereochemistry.  
 Double bond geometry as shown.

PAGE 1-A

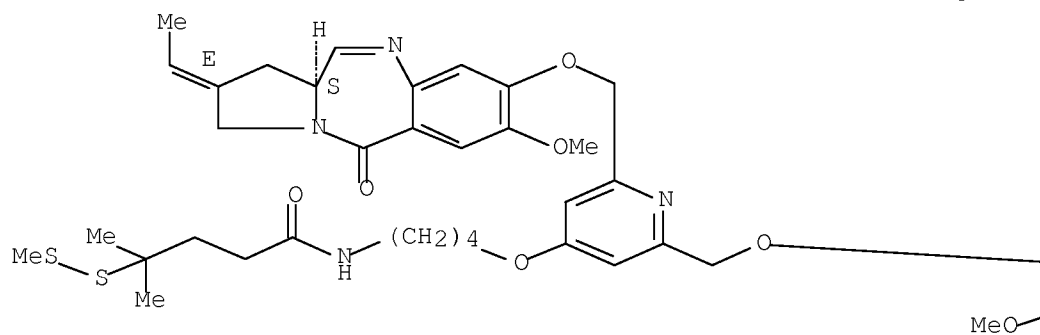


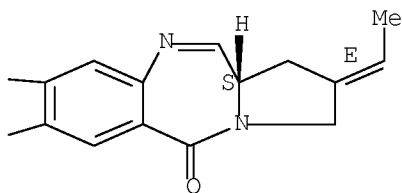


RN 945490-42-6 CAPLUS

CN Pentanamide, N-[4-[[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]-4-pyridinyl]oxy]butyl]-4-methyl-4-(methyldithio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

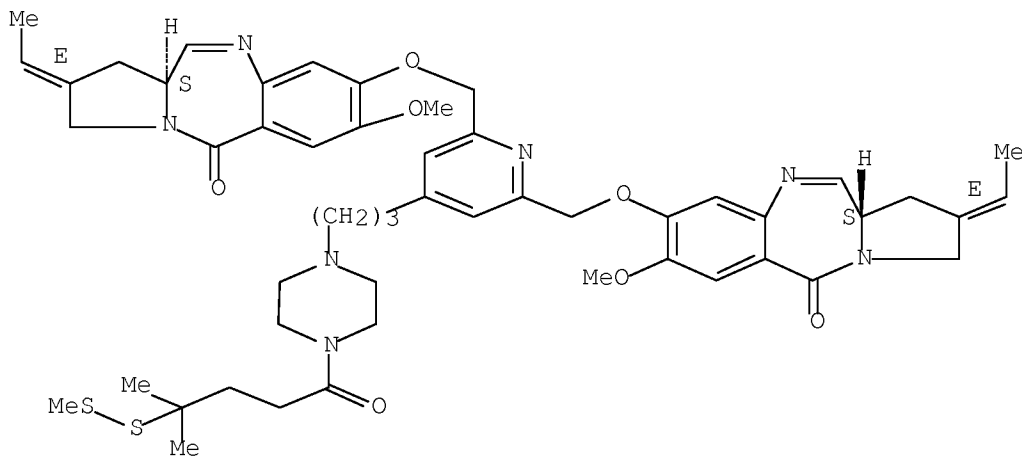




RN 945490-46-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[4-[3-[4-[4-methyl-4-(methyldithio)-1-oxopentyl]-1-piperazinyl]propyl]-2,6-pyridinediyl]bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

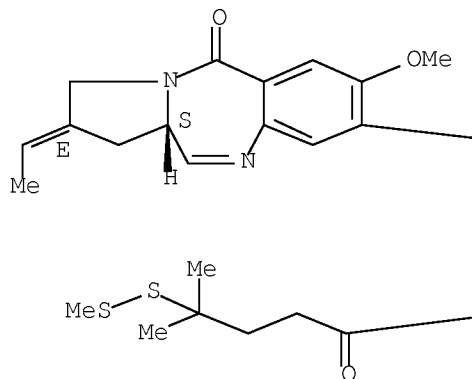


RN 945490-54-0 CAPLUS

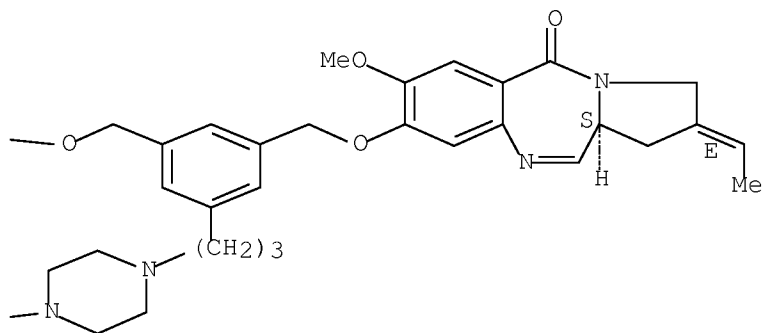
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[5-[3-[4-[4-methyl-4-(methyldithio)-1-oxopentyl]-1-piperazinyl]propyl]-1,3-phenylene]bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

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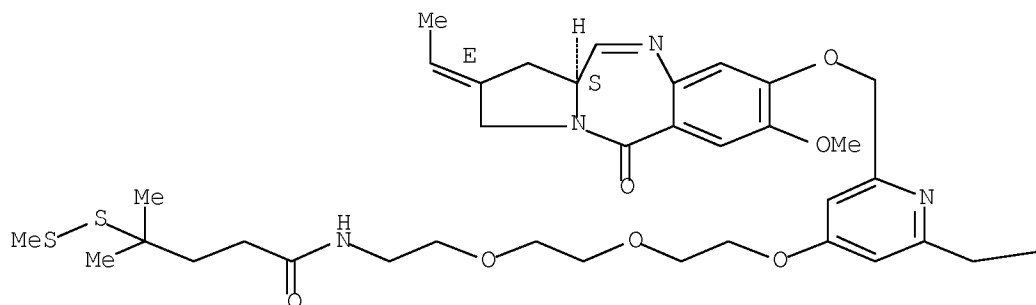
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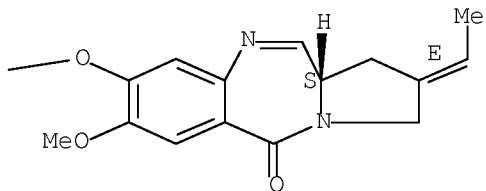


RN 945490-59-5 CAPLUS  
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Absolute stereochemistry.  
 Double bond geometry as shown.

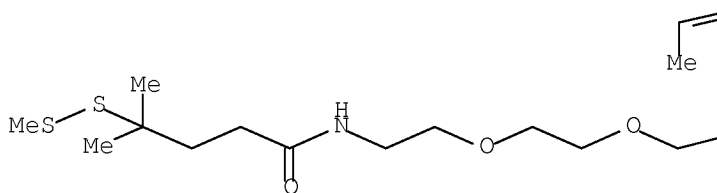
PAGE 1-A



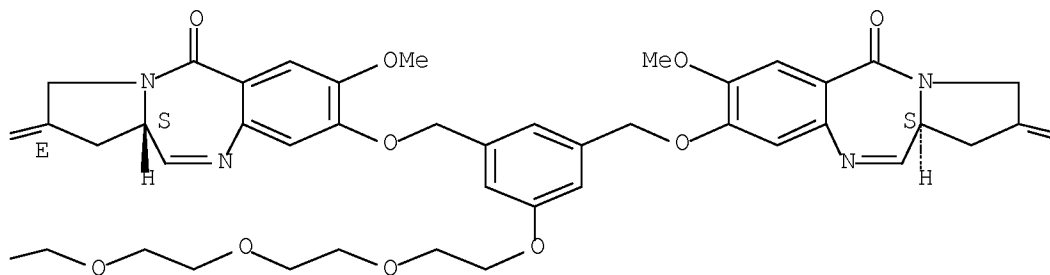


RN 945490-63-1 CAPLUS  
 CN Pentanamide, N-[17-[3,5-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenoxy]-3,6,9,12,15-pentaoxaheptadec-1-yl]-4-methyl-4-(methylthio)- (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as shown.



PAGE 1-B



PAGE 1-C

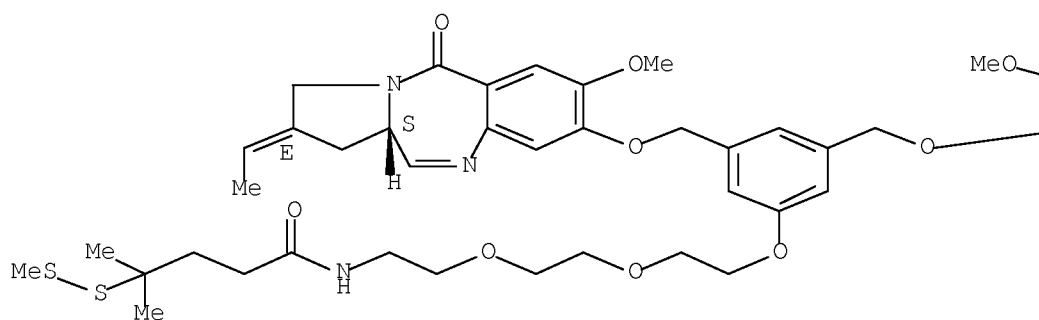


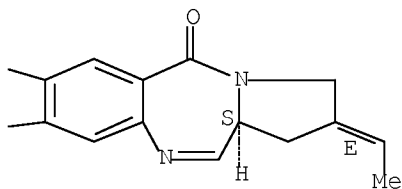
RN 945490-67-5 CAPLUS

CN Pentanamide, N-[2-[2-[2-[3,5-bis[[[(2E,11aS)-2-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenoxy]ethoxy]ethoxy]ethyl]-4-methyl-4-(methyldithio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A

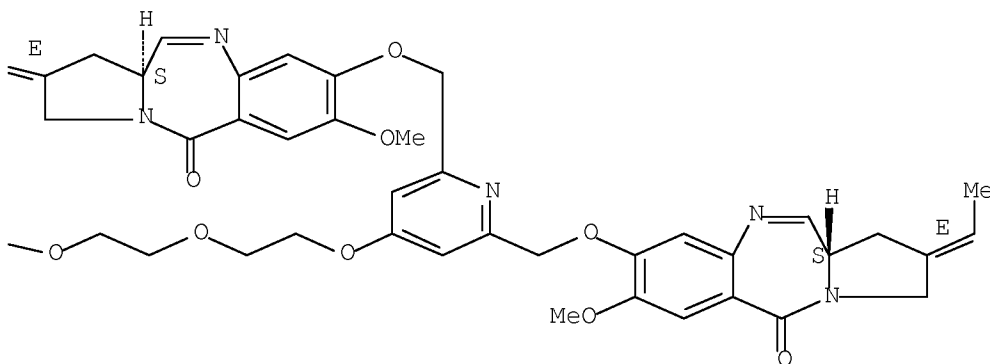
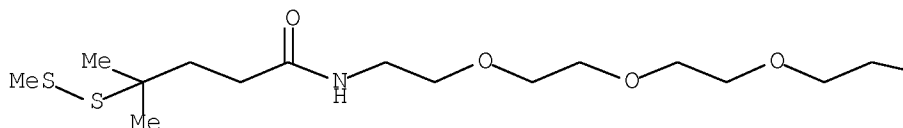




RN 945490-71-1 CAPLUS

CN Pentanamide, N-[17-[[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]-4-pyridinyl]oxy]-3,6,9,12,15-pentaoxaheptadec-1-yl]-4-methyl-4-(methyldithio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.



RN 945490-76-6 CAPLUS

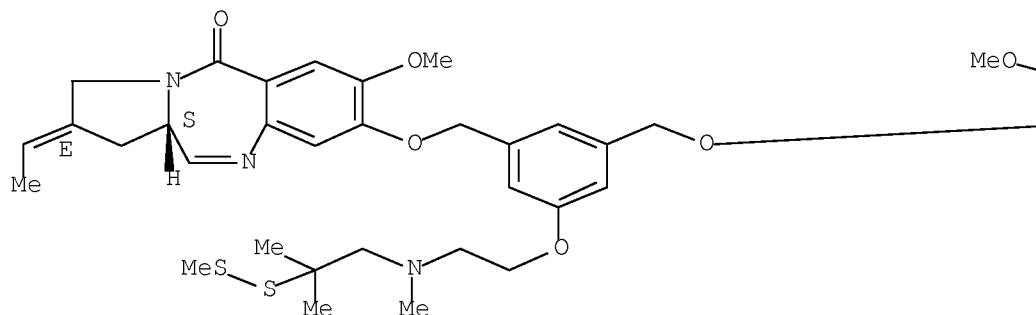
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[5-[2-[methyl[2-methyl-2-(methyldithio)propyl]amino]ethoxy]-1,3-phenylene]bis(methyleneoxy)]bis[2-



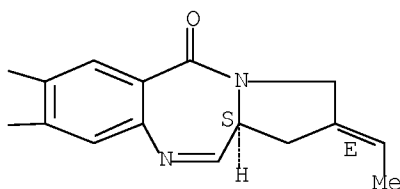
ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA  
INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A



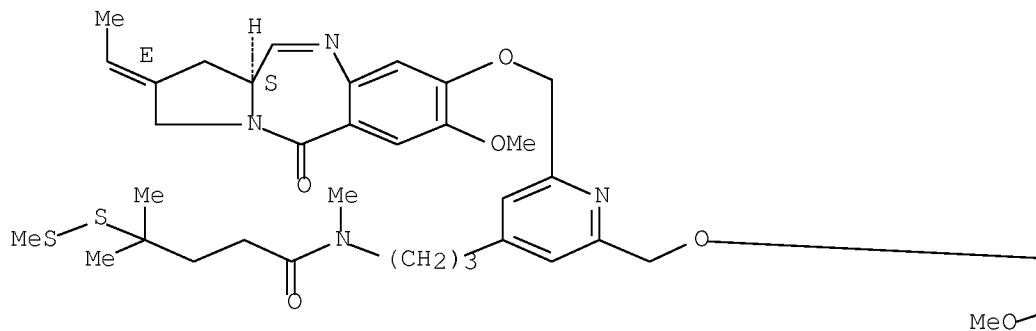
PAGE 1-B

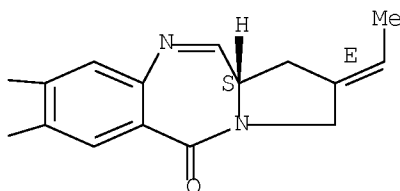


RN 945490-80-2 CAPLUS  
CN Pentanamide, N-[3-[2,6-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]-4-pyridinyl]propyl]-N,4-dimethyl-4-(methyldithio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A

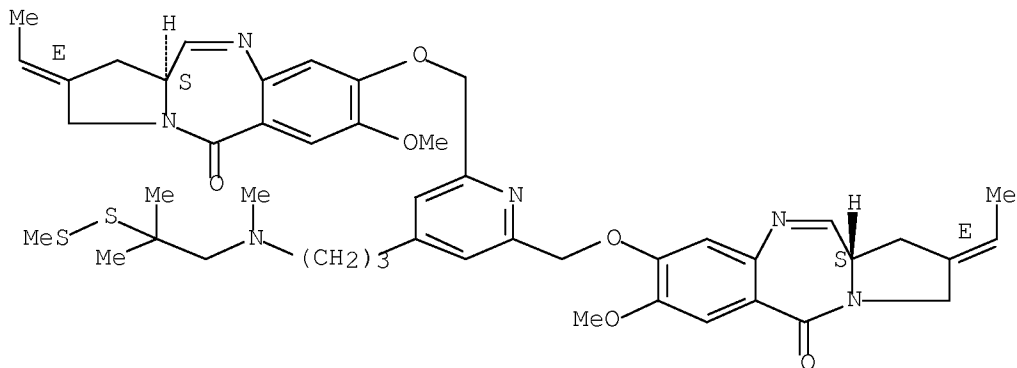




RN 945490-85-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[4-[3-[methyl[2-methyl-2-(methyldithio)propyl]amino]propyl]-2,6-pyridinediyl]bis(methyleneoxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

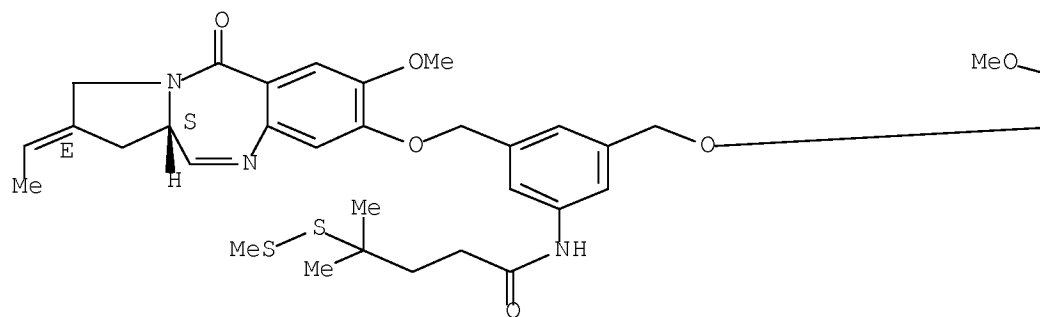


RN 945490-88-0 CAPLUS

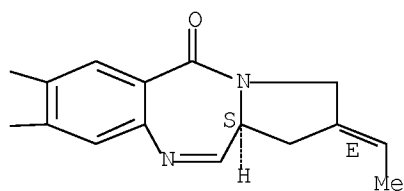
CN Pentanamide, N-[3,5-bis[[[(11aS)-2-(2E)-ethylidene-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]methyl]phenyl]-4-methyl-4-(methyldithio)- (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 10 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2007:752932 CAPLUS Full-text

DN 147:439621

TI Fludarabine-mediated suppression of the excision repair enzyme ERCC1 contributes to the cytotoxic synergy with the DNA minor groove crosslinking agent SJG-136 (NSC 694501) in chronic lymphocytic leukemia cells

AU Pepper, C.; Lowe, H.; Fegan, C.; Thurieau, C.; Thurston, D. E.; Hartley, J. A.; Delavault, P.

CS Department of Haematology, School of Medicine, Cardiff University, Cardiff, UK

SO British Journal of Cancer (2007), 97(2), 253-259  
CODEN: BJCAAI; ISSN: 0007-0920

PB Nature Publishing Group

DT Journal

LA English

AB In this study, we set out to establish whether fludarabine could enhance the DNA interstrand crosslinking capacity of SJG-136 in primary human chronic lymphocytic leukemia (CLL) cells and thereby offer a rationale for its clin. use in combination with SJG-136. SJG-136 rapidly induced DNA crosslinking in primary CLL cells which was concentration-dependent. Further, the level of crosslinking correlated with sensitivity to SJG-136-induced apoptosis ( $P = 0.001$ ) and higher levels of crosslinking were induced by the combination of SJG-136 and fludarabine ( $P = 0.002$ ). All of the samples tested ( $n = 40$ ) demonstrated synergy between SJG-136 and fludarabine (mean combination index (CI) =  $0.54 \pm 0.2$ ) and this was even retained in samples derived from patients with fludarabine resistance (mean CI =  $0.62 \pm 0.3$ ). Transcription of the excision repair enzyme, ERCC1, was consistently increased (20/20) in response to SJG-136 ( $P < 0.0001$ ). In contrast, fludarabine suppressed ERCC1 transcription ( $P = 0.04$ ) and inhibited SJG-136-induced ERCC1 transcription when used in combination ( $P = 0.001$ ). Importantly, the ability of fludarabine to suppress ERCC1 transcription correlated with the degree of synergy observed between SJG-136 and fludarabine ( $r^2 = 0.28$ ;  $P = 0.017$ ) offering a mechanistic rationale for the synergistic interaction. The data presented here provides a clear indication that this combination of drugs may have clin. utility as salvage therapy in drug-resistant CLL.

IT 232931-57-6, SJG-136

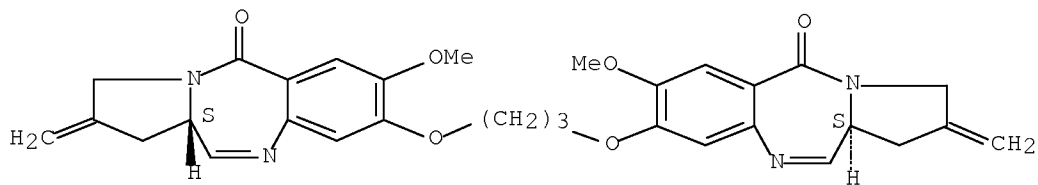
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(SJG-136-induced cytotoxicity due to DNA crosslinking was enhanced with fludarabine by suppression of transcription of excision repair enzyme ERCC1 gene in human primary chronic lymphocytic leukemia cell)

RN 232931-57-6 CAPLUS

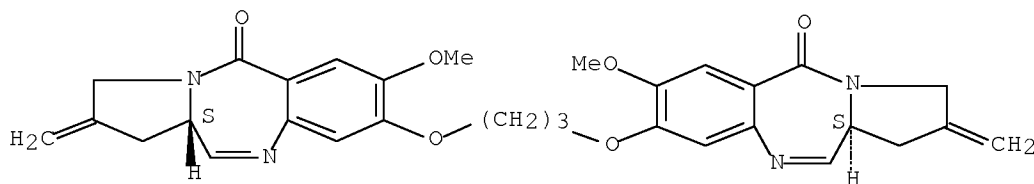
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



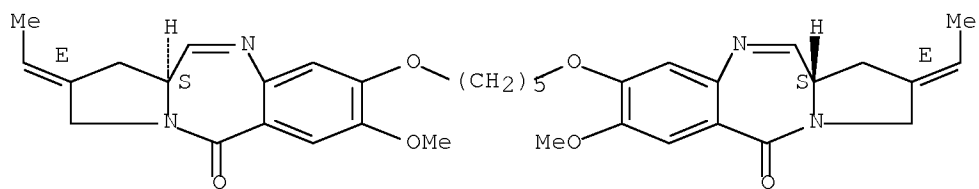
L18 ANSWER 11 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2007:522395 CAPLUS Full-text  
 DN 147:25489  
 TI Interactions of pyrrolobenzodiazepine dimers and duplex DNA from  
 methicillin-resistant Staphylococcus aureus  
 AU Hadjivassileva, Tsveta; Stapleton, Paul D.; Thurston, David E.; Taylor,  
 Peter W.  
 CS School of Pharmacy, London, WC1N 1AX, UK  
 SO International Journal of Antimicrobial Agents (2007), 29(6), 672-678  
 CODEN: IAAGEA; ISSN: 0924-8579  
 PB Elsevier B.V.  
 DT Journal  
 LA English  
 AB Binding of two bactericidal pyrrolobenzodiazepine (PBD) dimers, SJG-136 and  
 ELB-21, to genomic DNA from Staphylococcus aureus EMRSA-16 was investigated.  
 Both agents cross-linked purified EMRSA-16 DNA. The more potent agent, ELB-  
 21, had a greater capacity to cross-link DNA after incubation with intact  
 cells than SJG-136. Extensive interstrand crosslinking at multiple sites on  
 the EMRSA-16 genome was demonstrated by probing EcoRI-restricted DNA with mecA  
 and 16S rDNA. Crosslinking was again greater in DNA extracted from ELB-21-  
 treated cells and was compatible with frequency anal. of preferred binding  
 sequences in EMRSA-16 DNA. These studies support the premise that the potency  
 of ELB-21 is due to efficient cell penetration and provide evidence that the  
 antibacterial activity of PBD dimers results from crosslinking at specific  
 genomic sites.  
 IT 232931-57-6, SJG-136 877659-86-4, ELB-21  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (interactions of pyrrolobenzodiazepine dimers and duplex DNA from  
 methicillin-resistant Staphylococcus aureus)  
 RN 232931-57-6 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
 propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-,  
 (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 877659-86-4 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-  
 pentanediylbis(oxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-,  
 (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

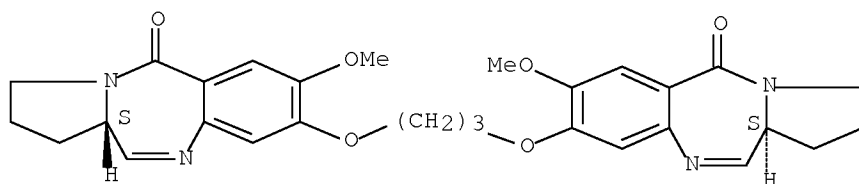
Absolute stereochemistry.  
 Double bond geometry as shown.



RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

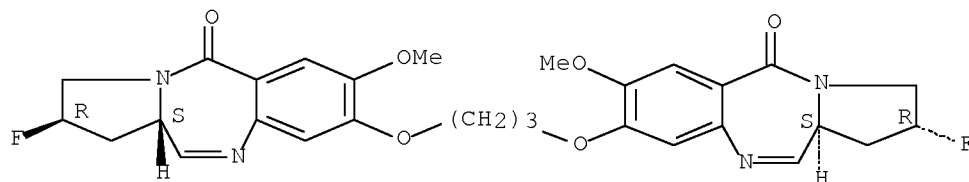
L18 ANSWER 12 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2007:81265 CAPLUS Full-text  
 DN 146:316881  
 TI Synthesis and DNA-binding ability of C2R-fluoro substituted DC-81 and its dimers  
 AU Kamal, Ahmed; Reddy, D. Rajasekhar; Reddy, P. S. Murali Mohan  
 CS Biotransformation Laboratory, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad, 500007, India  
 SO Bioorganic & Medicinal Chemistry Letters (2007), 17(3), 803-806  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Ltd.  
 DT Journal  
 LA English  
 OS CASREACT 146:316881  
 AB C2R-Fluoro substituted DC-81 and its dimers have been synthesized that exhibit significant DNA-binding ability, particularly the five carbon alkane spacer compound (6c) showed the helix melting temperature ( $\Delta T_m$ ) of 18.8 °C after incubation of 36 h at 37 °C.  
 IT 140676-21-7P 929049-25-2P 929049-27-4P 929049-29-6P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (synthesis and calf thymus DNA-binding of C2R-fluoro substituted DC-81 and its dimers)  
 RN 140676-21-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 929049-25-2 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2R,2'R,11aS,11'aS)-(CA INDEX NAME)

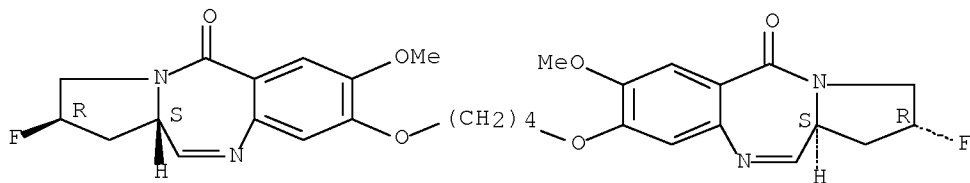
Absolute stereochemistry.



RN 929049-27-4 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2R,2'R,11aS,11'aS)- (CA INDEX NAME)

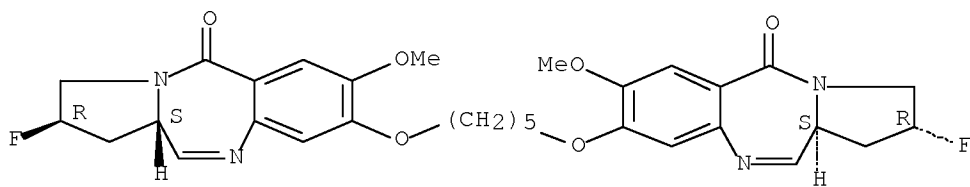
Absolute stereochemistry.



RN 929049-29-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediyibis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2R,2'R,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



L18 ANSWER 13 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2007:18760 CAPLUS Full-text

DN 146:197626

TI The hollow fibre model - facilitating anti-cancer pre-clinical pharmacodynamics and improving animal welfare

AU Suggitt, Marie; Cooper, Patricia A.; Shnyder, Steven D.; Bibby, Michael C.

CS Institute of Cancer Therapeutics, University of Bradford, Bradford, BD7 1DP, UK

SO International Journal of Oncology (2006), 29(6), 1493-1499

CODEN: IJONES; ISSN: 1019-6439

PB International Journal of Oncology

DT Journal

LA English

AB We describe a modified hollow fiber assay (HFA) for investigating the potential of novel mols. as pharmaceutical agents. In particular the assay provides drug/target interaction data that can facilitate the selection of lead compds. for further evaluation in more sophisticated solid tumor models, while successfully implementing the 3Rs - the 'replacement' 'refinement' and 'reduction' of animals. This more ethical and rapid approach to early drug development does not compromise on the validity, sensitivity, predictivity or efficacy of preclin. evaluation. We present novel data using the standard cross-linker mitomycin C (MMC) as a pos. control, and two investigational DNA interactive mols. (C1311/SJG-136). Tumor cells were seeded in fibers and implanted into mice. Following treatment with an i.p. injection, fibers were excised and cells retrieved for pharmacodynamic anal. using the comet assay/fluorescence microscopy. Microscopy results revealed nuclear uptake and localization within cytoplasmic organelles of HT29 colorectal adenocarcinoma cells following treatment with C1311 (150 mg/kg). Following treatment with SJG-136 (0.3 mg/kg) a 27.3% ( $p < 0.001$ ) DNA crosslinking (s.c.) effect was observed in the HL60 acute promyelocytic leukemia cell line. DNA crosslinking effects of 55% (i.p) and 50% (s.c.) ( $p < 0.005$ ) were observed in the A549 lung carcinoma cell line following administration of MMC (6 mg/kg). These data are consistent with previous activity defined using solid tumor models, and support the use of the HFA for in vivo pharmacodynamic investigation while significantly reducing animal nos. and the influence of tumor growth on the welfare of mice.

IT 232931-57-6, SJG-136

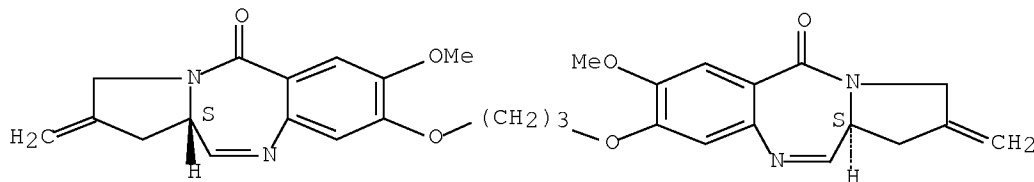
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(DNA crosslinking effect of SJG-136 was observed in human promyelocytic leukemia cells seeded hollow fibers in mouse)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 14 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2006:1124678 CAPLUS Full-text

DN 145:455035

TI Preparation of pyrrolobenzodiazepine derivatives for treatment of  
proliferative diseases

IN Gregson, Stephen John; Howard, Philip Wilson; Chen, Zhizhi

PA Spirogen Limited, UK

SO PCT Int. Appl., 77pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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	CA 2604805	A1	20061026	CA 2006-2604805	20060421
	GB 2439881	A	20080109	GB 2007-20721	20060421
	EP 1879901	A1	20080123	EP 2006-726846	20060421
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	IN 2007DN07862	A	20071109	IN 2007-DN7862	20071011
	CN 101171257	A	20080430	CN 2006-80015716	20071108
	KR 2008004618	A	20080109	KR 2007-727047	20071120
PRAI	GB 2005-8084	A	20050421		
	GB 2005-22746	A	20051107		
	WO 2006-GB1456	W	20060421		
OS	MARPAT 145:455035				
GI					

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The title compds. with general formula I [wherein: R2 = (un)substituted aryl;  
R6 and R9 = independently H, R, OH, OR, SH, SR, NH2, NHR, NRR', nitro, Me3Sn,  
or halo, where R and R' = independently (un)substituted alkyl, heterocyclyl,  
or aryl; R7 = H, R, OH, OR, SH, SR, NH2, NHR, NHRR', nitro, Me3Sn, or halo; Z  
= alkylene; X = O, S, or NH; n = 2 or 3] or pharmaceutically acceptable salts  
or solvates thereof are prepared for the treatment of proliferative diseases.  
For example, compound II•2Na was prepared in a multi-step synthesis. II•2Na  
showed IC50 of 1.5 nM in the In Vitro cytotoxicity test with K562 human  
chronic myeloid leukemia cells.

IT 913262-11-0P 913262-12-1P 913262-13-2P

913262-14-3P 913262-15-4P 913262-16-5P

913262-17-6P 913262-18-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
(Uses)

(antiproliferative agent; preparation of pyrrolobenzodiazepine derivs. for

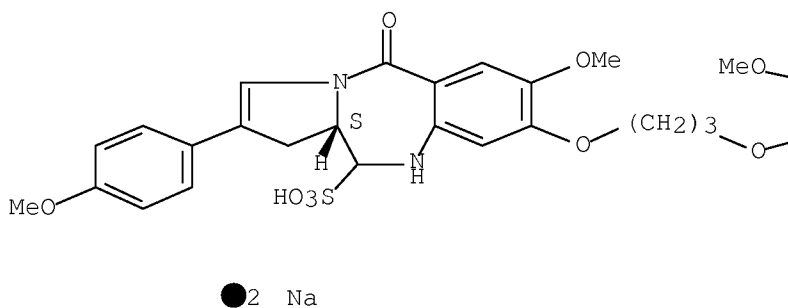
treatment of proliferative diseases)

RN 913262-11-0 CAPLUS

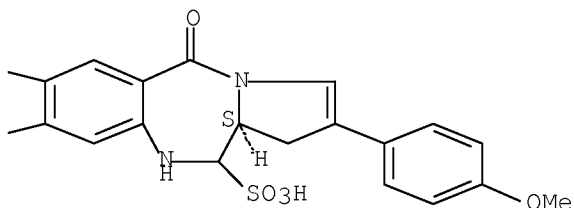
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-11-sulfonic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[5,10,11,11a-tetrahydro-7-methoxy-2-(4-methoxyphenyl)-5-oxo-, disodium salt, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

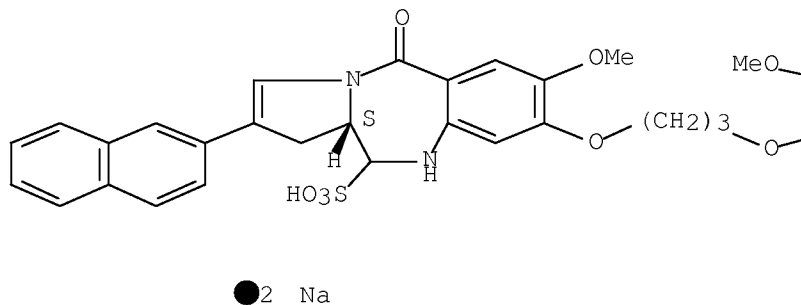


RN 913262-12-1 CAPLUS

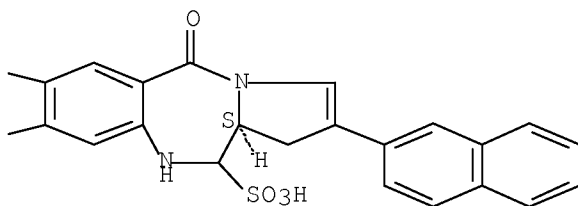
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-11-sulfonic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[5,10,11,11a-tetrahydro-7-methoxy-2-(2-naphthalenyl)-5-oxo-, disodium salt, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



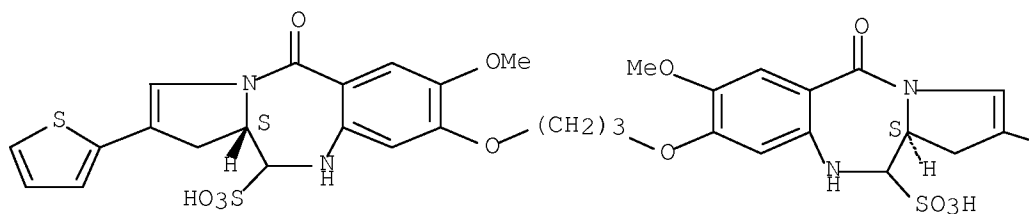
PAGE 1-B



RN 913262-13-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-11-sulfonic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[5,10,11,11a-tetrahydro-7-methoxy-5-oxo-2-(2-thienyl)-, disodium salt, (11aS,11'aS)- (9CI) (CA INDEX NAME)

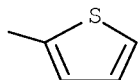
Absolute stereochemistry.

PAGE 1-A



● 2 Na

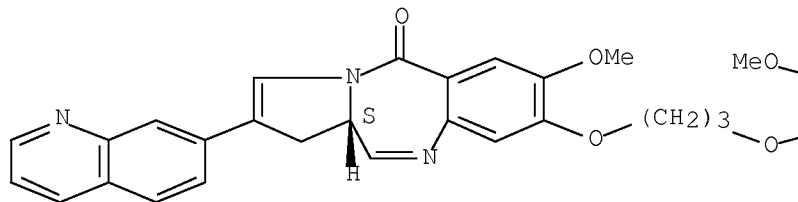
PAGE 1-B



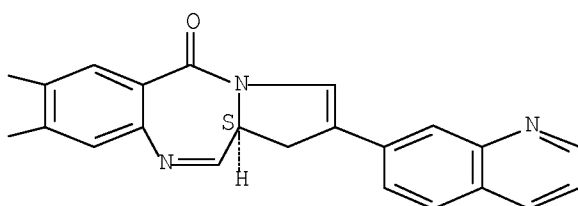
RN 913262-14-3 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,11a-dihydro-7-methoxy-2-(7-quinolinyl)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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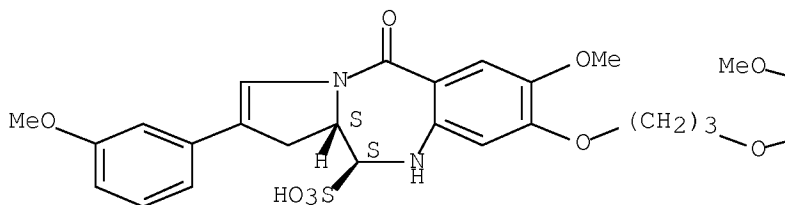
PAGE 1-B



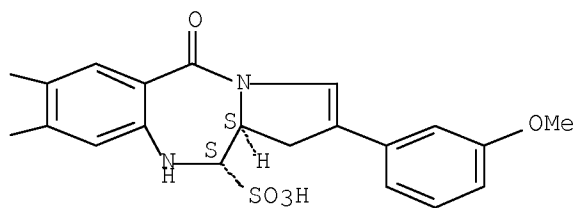
RN 913262-15-4 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-11-sulfonic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[5,10,11,11a-tetrahydro-7-methoxy-2-(3-  
 methoxyphenyl)-5-oxo-, disodium salt, (11S,11'S,11aS,11'aS)- (9CI) (CA  
 INDEX NAME)

Absolute stereochemistry.

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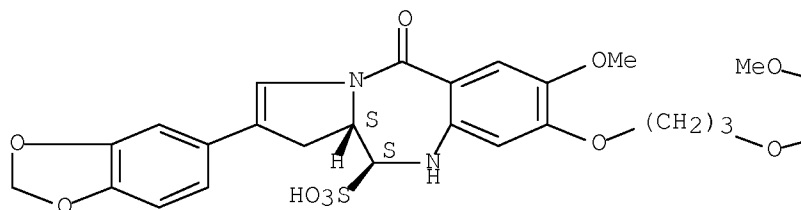
● 2 Na



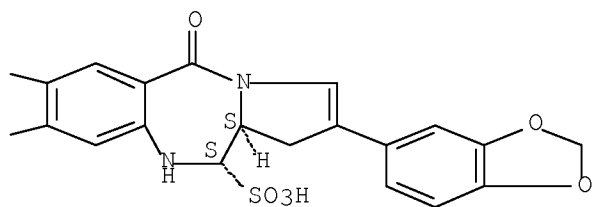
RN 913262-16-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-11-sulfonic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2-(1,3-benzodioxol-5-yl)-5,10,11,11a-  
tetrahydro-7-methoxy-5-oxo-, disodium salt, (11S,11'S,11aS,11'aS)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.



●2 Na

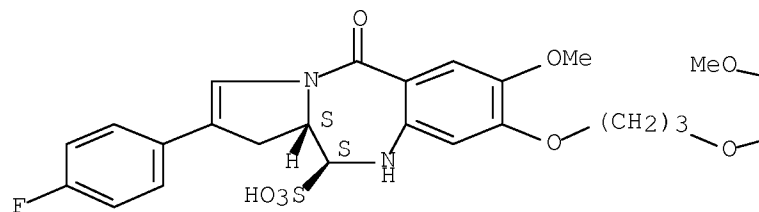


RN 913262-17-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-11-sulfonic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2-(4-fluorophenyl)-5,10,11,11a-  
tetrahydro-7-methoxy-5-oxo-, disodium salt, (11S,11'S,11aS,11'aS)- (9CI)  
(CA INDEX NAME)

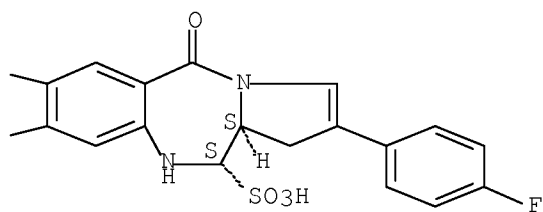
Absolute stereochemistry.

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● 2 Na

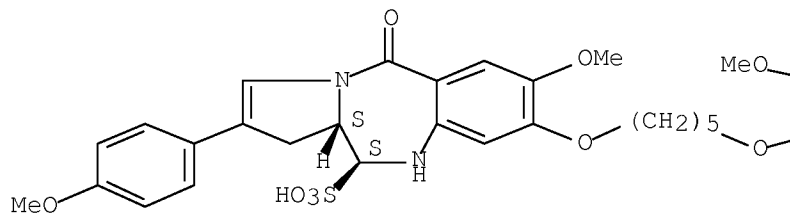
PAGE 1-B



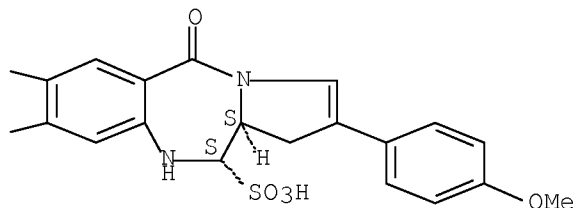
RN 913262-18-7 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-11-sulfonic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[5,10,11,11a-tetrahydro-7-methoxy-2-(4-  
 methoxyphenyl)-5-oxo-, disodium salt, (11S,11'S,11aS,11'aS)- (9CI) (CA  
 INDEX NAME)

Absolute stereochemistry.

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● 2 Na



IT 913262-20-1P 913262-22-3P 913262-25-6P  
913262-27-8P 913262-29-0P

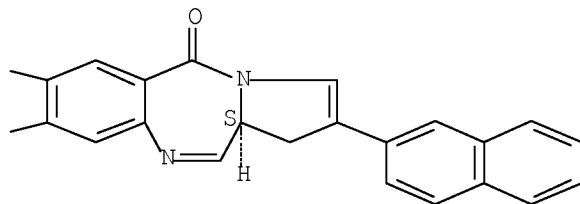
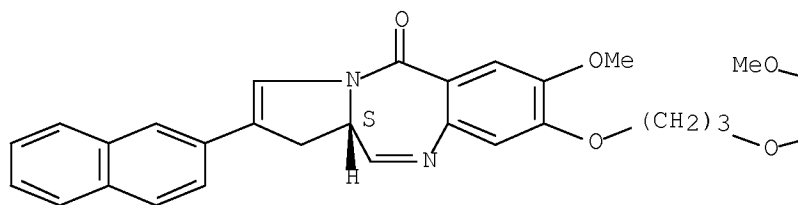
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of pyrrolobenzodiazepine derivs. for treatment of proliferative diseases)

RN 913262-20-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,11a-dihydro-7-methoxy-2-(2-naphthalenyl)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



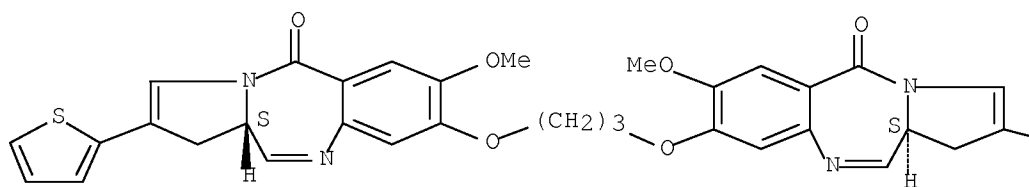
RN 913262-22-3 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,11a-dihydro-7-methoxy-2-(2-thienyl)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

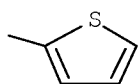
Absolute stereochemistry.



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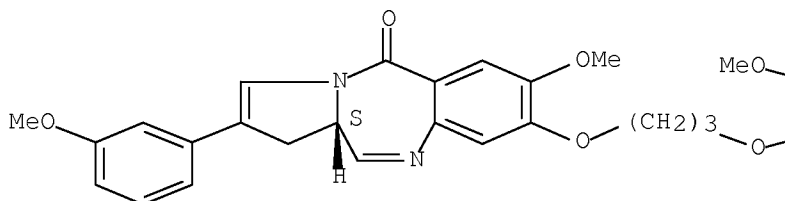
PAGE 1-B



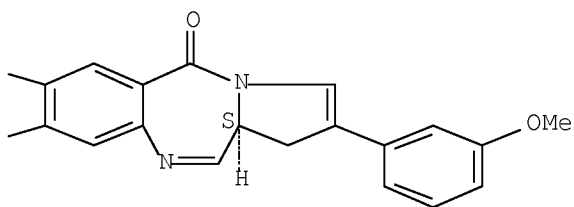
RN 913262-25-6 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,11a-dihydro-7-methoxy-2-(3-methoxyphenyl)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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RN 913262-27-8 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-

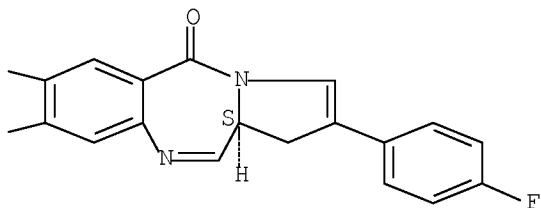
Absolute stereochemistry.

COC1=CC=C2C(=C1)N=C(S[C@H]3C=C(C=C3)C4=CC=C5C(=C4)OC5OC6CCCC6OC)C(=O)N2C=O

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[2-(4-fluorophenyl)-1,11a-dihydro-7-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

COc1cc2c(c1)nc(s2)C3=CC=C(C=C3)C4=CC=C(C=C4)F



IT 864754-61-0P 864754-66-5P 864754-68-7P  
 864755-08-8P 864755-09-9P 864755-10-2P  
 864755-11-3P 913262-19-8P 913262-21-2P  
 913262-23-4P 913262-24-5P 913262-26-7P  
 913262-28-9P 913262-34-7P 913262-35-8P  
 913262-36-9P 913262-37-0P 913262-38-1P  
 913262-39-2P 913262-40-5P

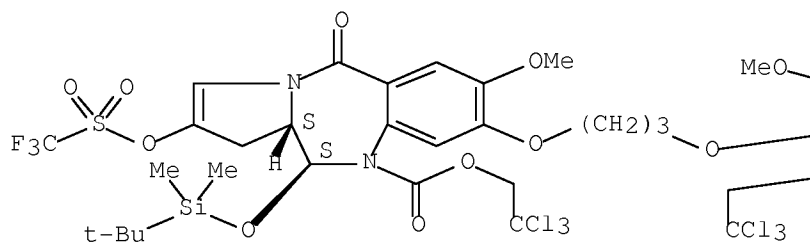
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)

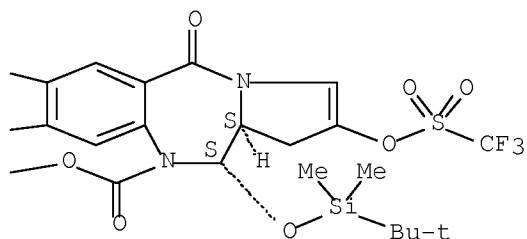
(preparation of pyrrolobenzodiazepine derivs. for treatment of  
 proliferative diseases)

RN 864754-61-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[[(1,1-dimethylethyl)dimethylsilyl]ox  
 y]-11,11a-dihydro-7-methoxy-5-oxo-2-[[[(trifluoromethyl)sulfonyl]oxy]-,  
 bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
 NAME)

Absolute stereochemistry. Rotation (+).

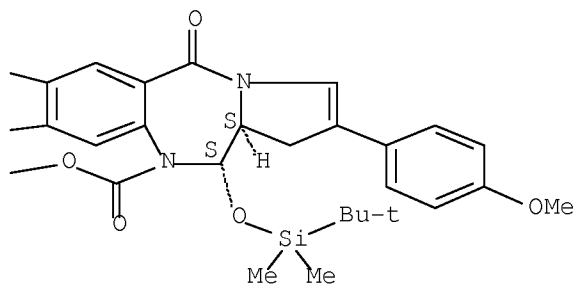
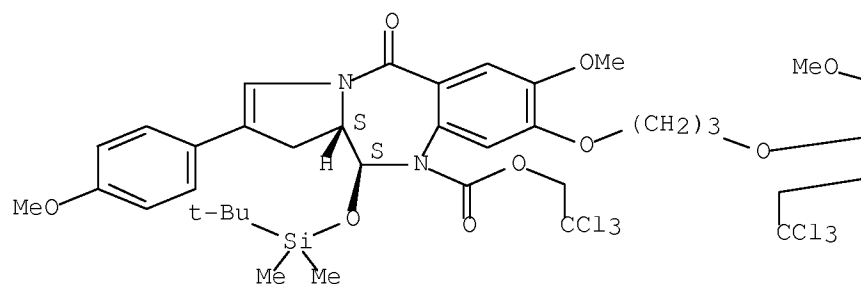




RN 864754-66-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[11-[(1,1-dimethylethyl)dimethylsilyl]ox  
y]-11,11a-dihydro-7-methoxy-2-(4-methoxyphenyl)-5-oxo-,  
bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
NAME)

Absolute stereochemistry.

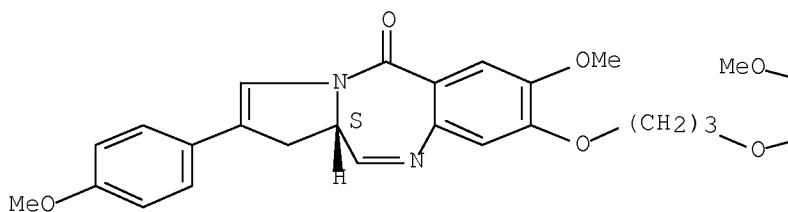


RN 864754-68-7 CAPLUS

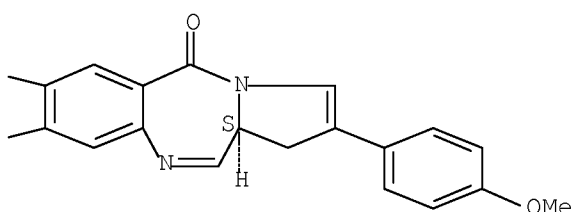
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
propanediylbis(oxy)]bis[1,11a-dihydro-7-methoxy-2-(4-methoxyphenyl)-,  
(11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

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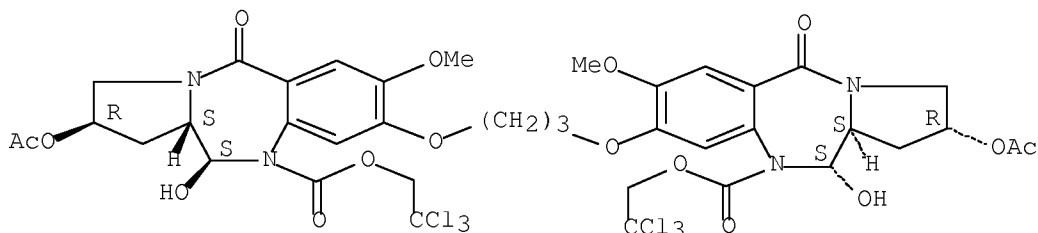
PAGE 1-B



RN 864755-08-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2-(acetyloxy)-2,3,11,11a-tetrahydro-11-  
hydroxy-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester,  
(2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

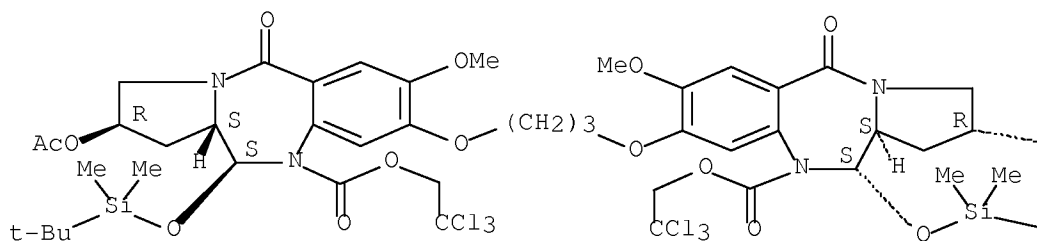
Absolute stereochemistry.



RN 864755-09-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2-(acetyloxy)-11-[[1,1-  
dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-,  
bis(2,2,2-trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA  
INDEX NAME)

Absolute stereochemistry.

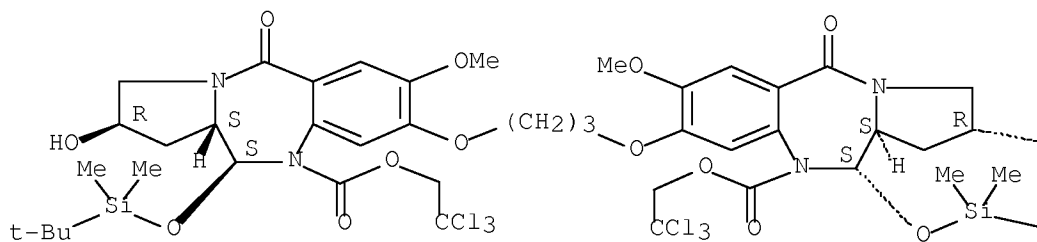


--- OAc

--- Bu-t

RN 864755-10-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[[(1,1-dimethylethyl)dimethylsilyl]ox  
 y]-2,3,11a-tetrahydro-2-hydroxy-7-methoxy-5-oxo-, bis(2,2,2-  
 trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
 NAME)

Absolute stereochemistry.



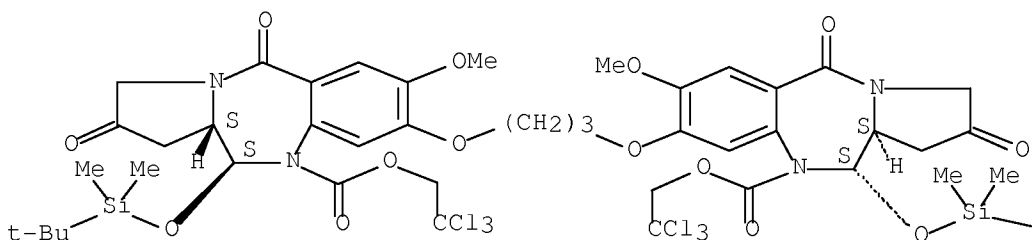
---OH

---Bu-t

RN 864755-11-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]oxy]  
-2,3,11,11a-tetrahydro-7-methoxy-2,5-dioxo-, bis(2,2,2-trichloroethyl)  
ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



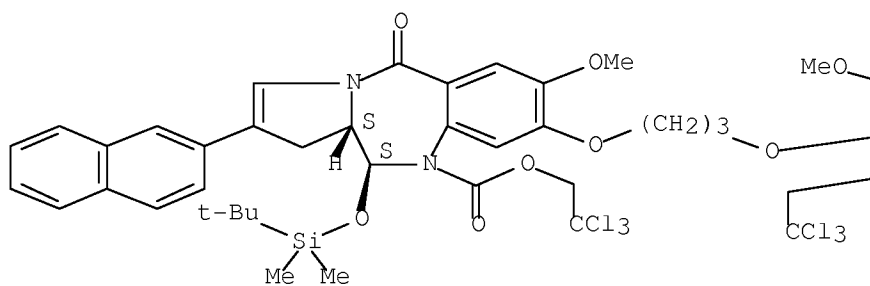
---Bu-t

RN 913262-19-8 CAPLUS

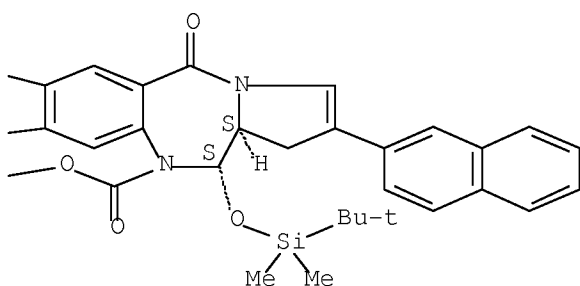
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]oxy]  
-11,11a-dihydro-7-methoxy-2-(2-naphthalenyl)-5-oxo-,  
bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
NAME)

Absolute stereochemistry.

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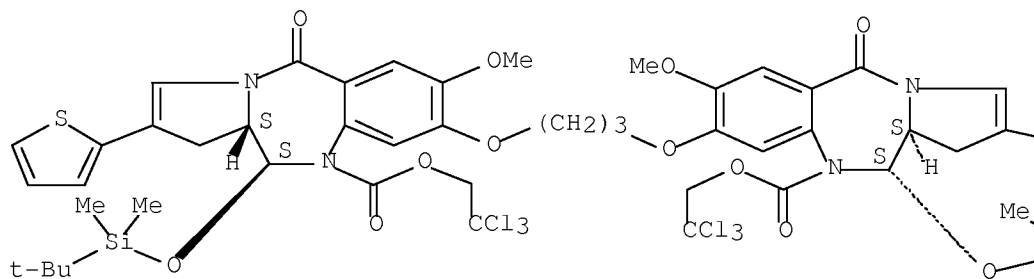
PAGE 1-B



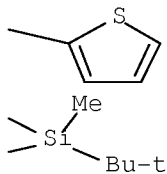
RN 913262-21-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[[(1,1-dimethylethyl)dimethylsilyl]ox  
 y]-11,11a-dihydro-7-methoxy-5-oxo-2-(2-thienyl)-, bis(2,2,2-  
 trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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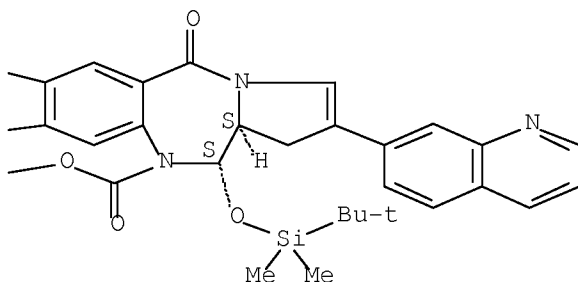
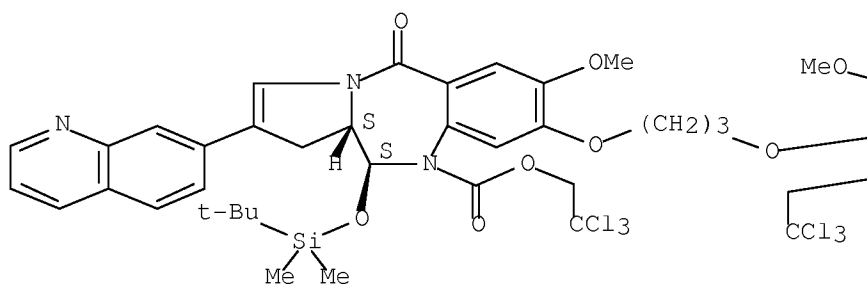




RN 913262-23-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]oxy]  
-11,11a-dihydro-7-methoxy-5-oxo-2-(7-quinolinyl)-, bis(2,2,2-  
trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



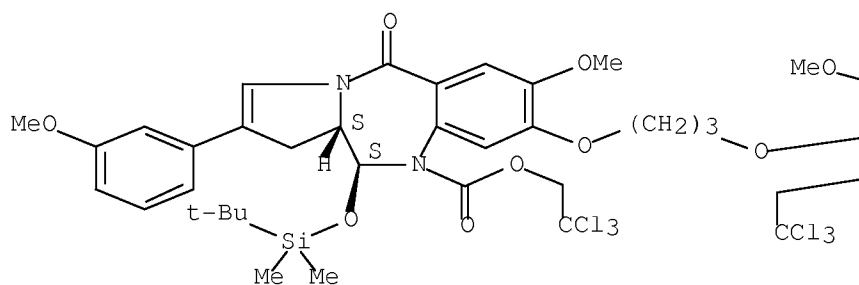
RN 913262-24-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]oxy]  
-11,11a-dihydro-7-methoxy-2-(3-methoxyphenyl)-5-oxo-,  
bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX

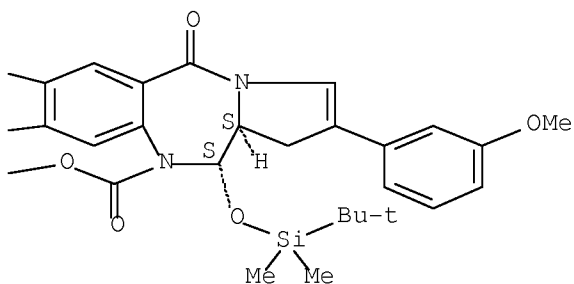
NAME)

Absolute stereochemistry.

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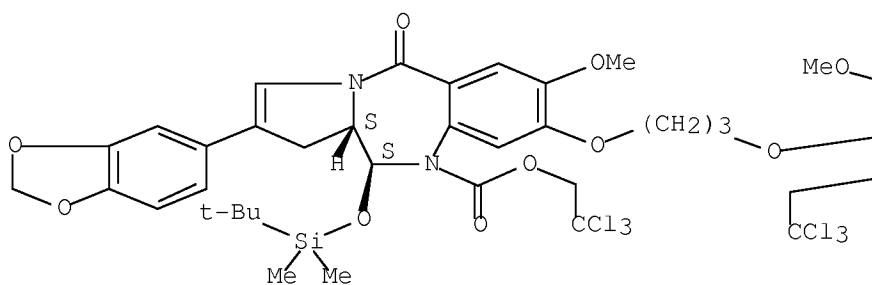
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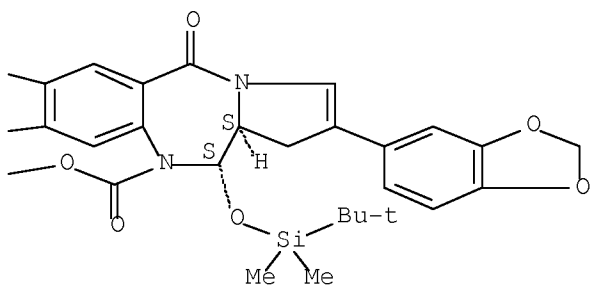


RN 913262-26-7 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2-(1,3-benzodioxol-5-yl)-11-[[ (1,1-  
dimethylethyl)dimethylsilyl]oxy]-11,11a-dihydro-7-methoxy-5-oxo-,  
bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
NAME)

Absolute stereochemistry.

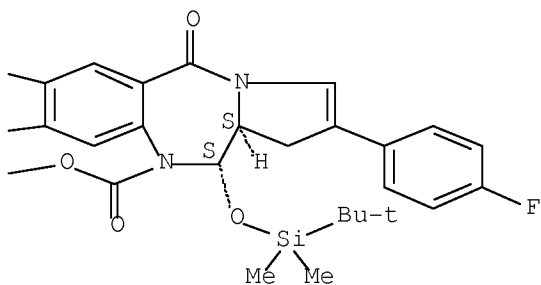
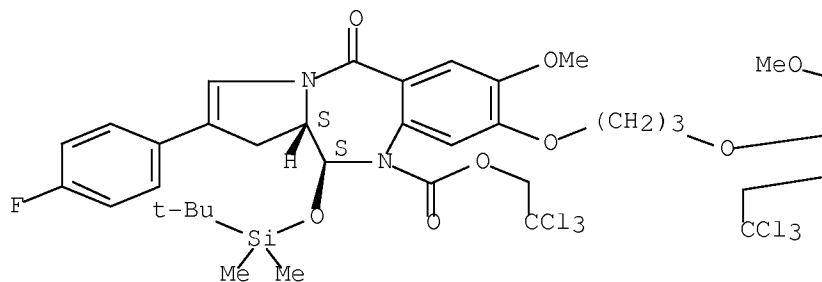
PAGE 1-A





RN 913262-28-9 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[ (1,1-dimethylethyl)dimethylsilyl]ox  
 y]-2-(4-fluorophenyl)-11,11a-dihydro-7-methoxy-5-oxo-,  
 bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
 NAME)

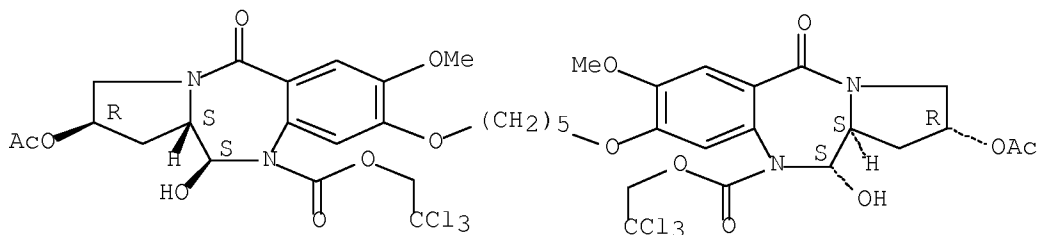
Absolute stereochemistry.



RN 913262-34-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,5-pentanediy]bis(oxy)]bis[2-(acetyloxy)-2,3,11,11a-tetrahydro-11-  
hydroxy-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester,  
(2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

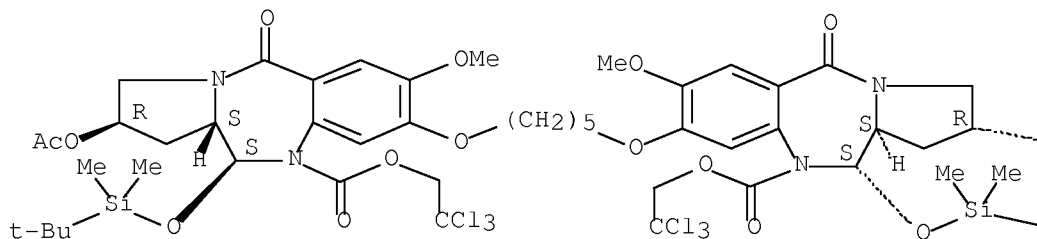


RN 913262-35-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,5-pentanediy]bis(oxy)]bis[2-(acetyloxy)-11-[[1,1-  
dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-,  
bis(2,2,2-trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA  
INDEX NAME)

Absolute stereochemistry.

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.....OAc

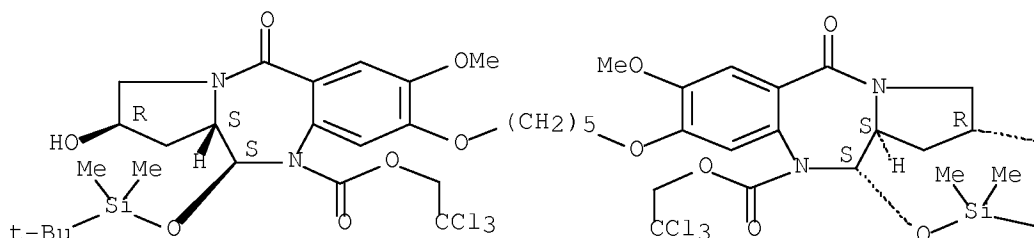
———Bu-t

RN 913262-36-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,5-pentanediy]bis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]ox  
 y]-2,3,11,11a-tetrahydro-2-hydroxy-7-methoxy-5-oxo-, bis(2,2,2-  
 trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
 NAME)

Absolute stereochemistry.

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OH

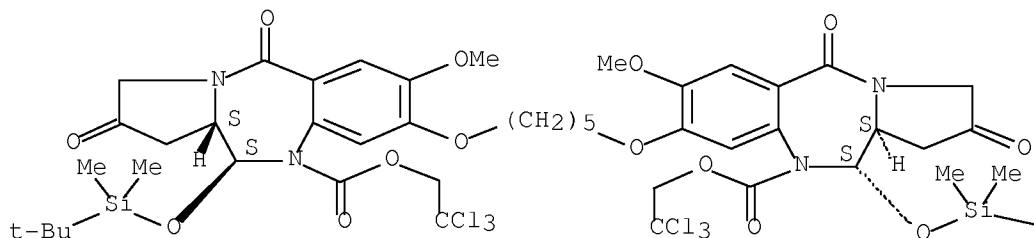
Bu-t

RN 913262-37-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,5-pentanediy]bis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]ox  
 y]-2,3,11,11a-tetrahydro-2-hydroxy-7-methoxy-2,5-dioxo-,  
 bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
 NAME)

Absolute stereochemistry.

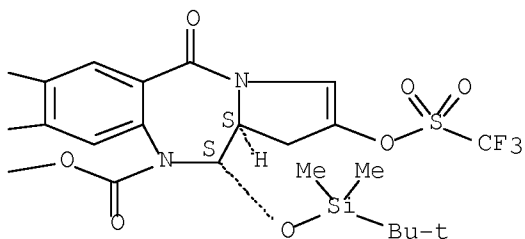
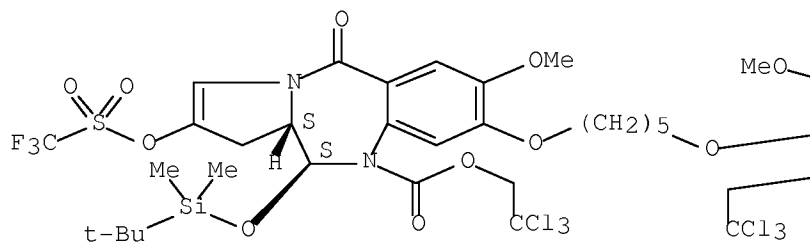
PAGE 1-A



—Bu-t

RN 913262-38-1 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,5-pentanediy]bis(oxy)]bis[11-[[ (1,1-dimethylethyl)dimethylsilyl]ox  
 y]-11,11a-dihydro-7-methoxy-5-oxo-2-[[ (trifluoromethyl)sulfonyl]oxy]-,  
 bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
 NAME)

Absolute stereochemistry.

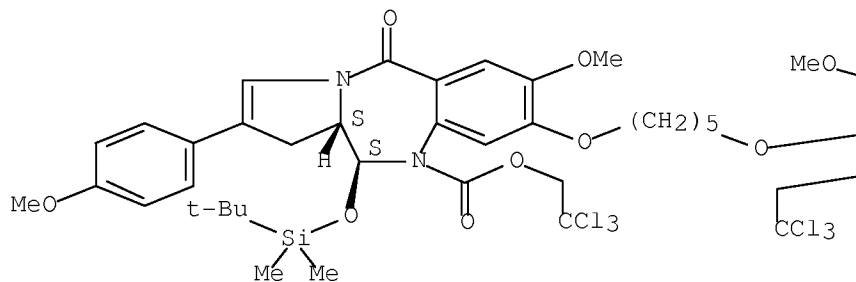


RN 913262-39-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,5-pentanediy]bis(oxy)]bis[11-[[ (1,1-dimethylethyl)dimethylsilyl]ox

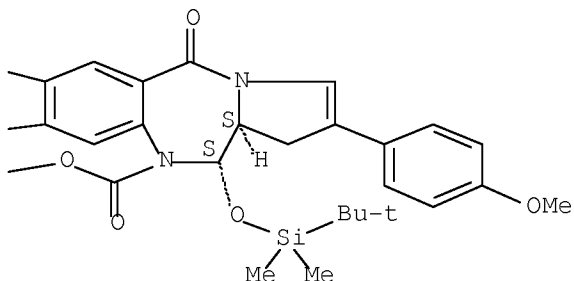
y]-11,11a-dihydro-7-methoxy-2-(4-methoxyphenyl)-5-oxo-,  
bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
NAME)

Absolute stereochemistry.

PAGE 1-A



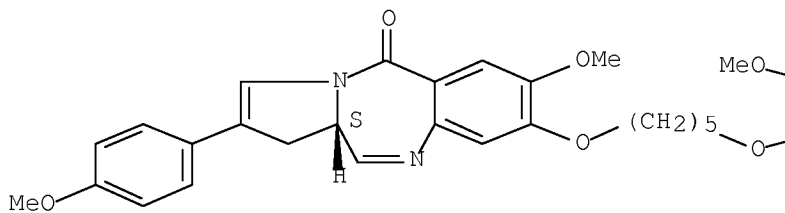
PAGE 1-B

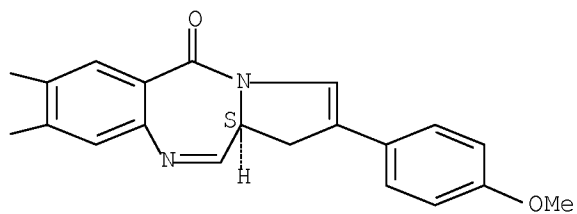


RN 913262-40-5 CAPLUS  
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-  
pentanediylbis(oxy)]bis[1,11a-dihydro-7-methoxy-2-(4-methoxyphenyl)-,  
(11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

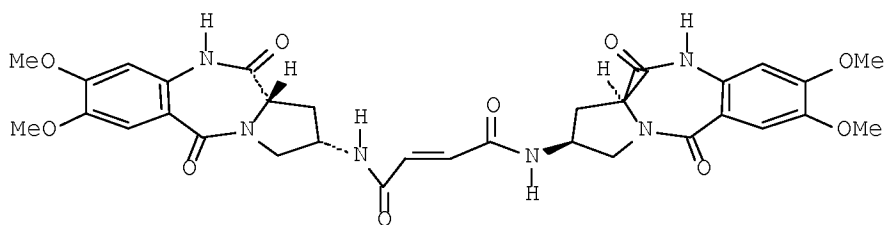




RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



L18 ANSWER 15 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2006:854897 CAPLUS Full-text  
 DN 145:419101  
 TI Facile synthesis of pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione dimer  
 AU Al-Said, Naim H.  
 CS Department of Applied Chemical Sciences, Jordan University of Science and  
 Technology, Irbid, 22110, Jordan  
 SO Journal of Heterocyclic Chemistry (2006), 43(4), 1091-1093  
 CODEN: JHTCAD; ISSN: 0022-152X  
 PB HeteroCorporation  
 DT Journal  
 LA English  
 OS CASREACT 145:419101  
 GI

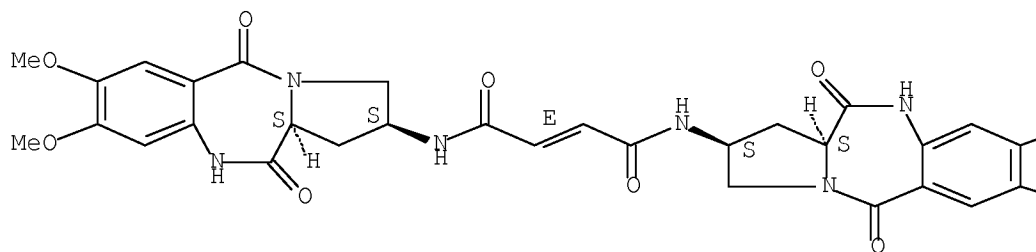


I

AB Efficient synthesis of a biol. important pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione dimer (I) linked through the C-2 positions by fumarate group is described.  
 IT 912289-35-1F  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione dimer)  
 RN 912289-35-1 CAPLUS  
 CN 2-Butenediamide, N1,N4-bis[(2S,11aS)-2,3,5,10,11,11a-hexahydro-7,8-dimethoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]-, (2E)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
 Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

—OMe

—OMe

RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 16 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2006:830168 CAPLUS Full-text

DN 145:336030

TI An efficient solid-phase synthesis of biologically important DNA-interactive pyrrolo[2,1-c][1,4]benzodiazepine dimers (DSB-120) and their C2-fluorinated analogues

AU Kamal, Ahmed; Shankaraiah, N.; Devaiah, V.; Reddy, K. Laxma

CS Biotransformation Laboratory, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad, 500 007, India

SO Tetrahedron Letters (2006), 47(37), 6553-6556

CODEN: TELEAY; ISSN: 0040-4039

PB Elsevier Ltd.

DT Journal

LA English

OS CASREACT 145:336030

AB A facile method for the solid-phase synthesis of pyrrolo[2,1-c][1,4]benzodiazepine dimers has been developed. Wang resin bound 4-nitrophenyl carbonate attached to 2-amino-5-methoxy-Me benzoate has been utilized as the resin-bound starting material and these reactions are monitored by FT-IR spectroscopy of resin beads.

IT 140676-21-7P 145325-56-0P 145325-57-1P

717920-82-6P 717920-83-7P 717920-84-8P

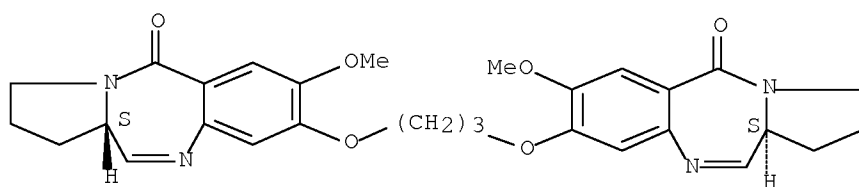
RL: SPN (Synthetic preparation); PREP (Preparation)

(solid phase synthesis of chiral pyrrolobenzodiazepine dimers and fluorinated analogs via amidation of resin bound nitrophenylcarbonate with bisaminobenzoates followed by hydrolysis, amidation, Swern oxidation, heterocyclization and cleavage)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

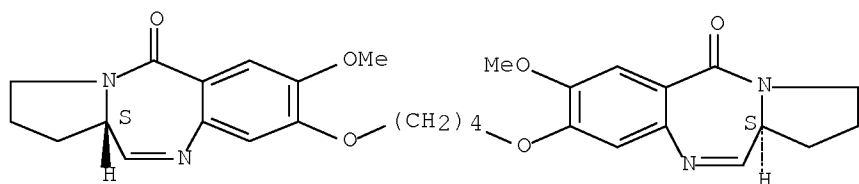
Absolute stereochemistry. Rotation (+).



RN 145325-56-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

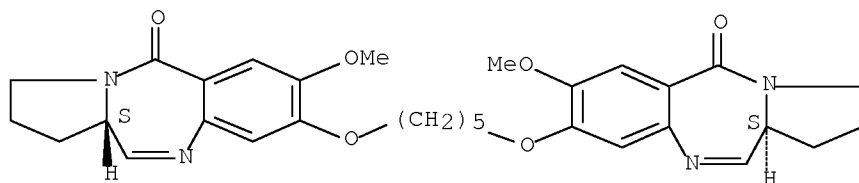
Absolute stereochemistry.



RN 145325-57-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediy]bis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

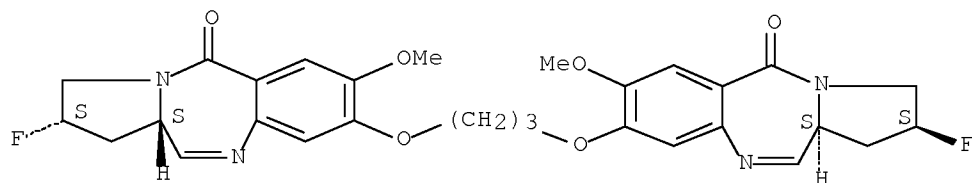
Absolute stereochemistry. Rotation (+).



RN 717920-82-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediyl]bis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

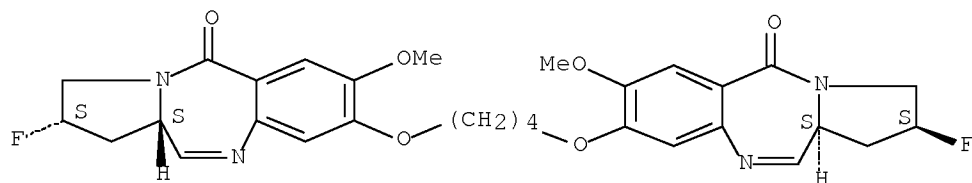
Absolute stereochemistry.



RN 717920-83-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediyl]bis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

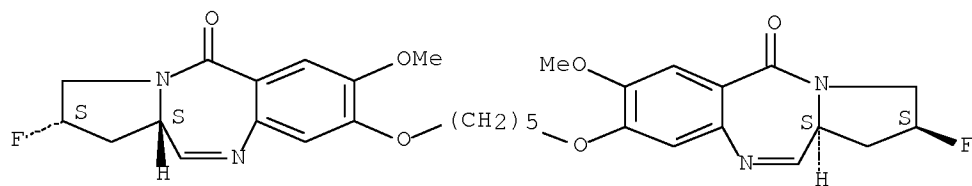
Absolute stereochemistry.



RN 717920-84-8 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediy]bis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 17 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2006:782707 CAPLUS Full-text

DN 145:305639

TI Design, Synthesis, and Biophysical and Biological Evaluation of a Series of Pyrrolobenzodiazepine-Poly(N-methylpyrrole) Conjugates

AU Wells, Geoff; Martin, Christopher R. H.; Howard, Philip W.; Sands, Zara A.; Laughton, Charles A.; Tiberghien, Arnaud; Woo, Chi Kit; Masterson, Luke A.; Stephenson, Marissa J.; Hartley, John A.; Jenkins, Terence C.; Shnyder, Steven D.; Loadman, Paul M.; Waring, Michael J.; Thurston, David E.

CS Cancer Research UK Gene Targeted Drug Design Research Group, The School of Pharmacy, University of London, London, WC1N 1AX, UK

SO Journal of Medicinal Chemistry (2006), 49(18), 5442-5461

CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

OS CASREACT 145:305639

AB A novel series of six Me ester-terminated C8-linked pyrrolobenzodiazepine (PBD)-poly(N-methylpyrrole) conjugates has been synthesized and their DNA interaction evaluated by thermal denaturation, DNA footprinting, and in vitro transcription stop assays. The synergistic effect of attaching a PBD unit to a polypyrrole fragment is illustrated by the large increase in DNA binding affinity (up to 50-fold) compared to the individual PBD and pyrrole components. The conjugates were found to bind mainly to identical DNA sequences but with apparent binding site widths increasing with mol. length and the majority of sites conforming to the consensus motif 5'-XGXWz (z = 3±1; W = A or T; X = any base but preferably a purine). They also provided robust sequence-selective blockade of transcription at sites corresponding approx. to their DNA footprints. The conjugates were shown to have good cellular/nuclear penetration properties, and a degree of correlation between cytotoxicity and DNA-binding affinity was observed

IT 232931-57-6, SJG-136

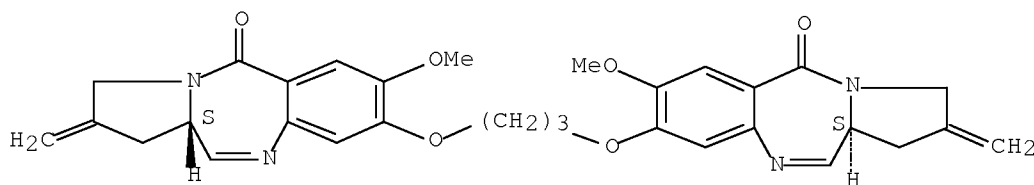
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(design, synthesis, and biophys. and biol. evaluation of a series of pyrrolobenzodiazepine-poly(N-methylpyrrole) conjugates)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L18 ANSWER 18 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2006:769518 CAPLUS Full-text

DN 145:347756

TI LC-MS/MS assay and dog pharmacokinetics of the dimeric pyrrolobenzodiazepine SJG-136 (NSC 694501)

AU Buhrow, Sarah A.; Reid, Joel M.; Jia, Lee; McGovern, Renee M.; Covey, Joseph M.; Kobs, Dean J.; Grossi, Irma M.; Ames, Matthew M.

CS Department of Oncology, Division of Developmental Oncology Research, Mayo Clinic and Foundation, Rochester, MN, 55905, USA

SO Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2006), 840(1), 56-62

CODEN: JCBAAI; ISSN: 1570-0232

PB Elsevier B.V.

DT Journal

LA English

AB The dimeric pyrrolobenzodiazepine SJG-136 (NSC 694501) has potent in vitro cytotoxicity and in vivo antitumor activity. SJG-136 binds in the minor groove of DNA and produces G-G interstrand cross-links via reactive N10-C11/N10'-C11' imine/carbinolamine moieties. We have developed a sensitive, specific liquid chromatog. tandem mass spectrometry (LC/MS/MS) method for the quant. determination of SJG-136 in plasma. SJG-136 was isolated by solid phase extraction through a C8 column, reverse-phase HPLC separation was accomplished on a C18 column with isocratic elution and MS/MS detection, monitoring the m/z 557-m/z 476 transition after electrospray ionization. The linear range and lower limit of quantitation from plasma standard curves were 2.8-1800 nM, and 5 nM, resp. SJG-136 plasma protein binding was species-dependent. Values of the unbound fraction in human, rat and mouse were 25%, 16.2% and <1%, resp. Protein binding was saturable in dog plasma where the unbound fraction increased from 10.8% to 22.3% over a 22-720 nM concentration range. SJG-136 pharmacokinetics after a single i.v. dose were best fit to a two-compartment open model with elimination half-life and plasma clearance values of 97 min and 6.1 mL/min/kg, resp. SJG-136 did not accumulate in plasma following i.v. administration of 1.0 µg/kg doses for five consecutive days.

IT 232931-57-6, NSC 694501

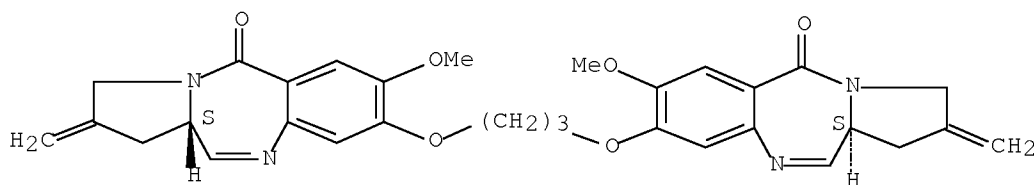
RL: ANT (Analyte); PKT (Pharmacokinetics); ANST (Analytical study); BIOL (Biological study)

(LC-MS/MS assay and dog pharmacokinetics of the dimeric pyrrolobenzodiazepine SJG-136 (NSC 694501))

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 19 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2006:701160 CAPLUS Full-text

DN 146:59804

TI Targeted disruption of FANCC and FANCG in human cancer provides a preclinical model for specific therapeutic options

AU Gallmeier, Eike; Calhoun, Eric S.; Rago, Carlo; Brody, Jonathan R.; Cunningham, Steven C.; Hucl, Tomas; Gorospe, Myriam; Kohli, Manu; Lengauer, Christoph; Kern, Scott E.

CS The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA

SO Gastroenterology (2006), 130(7), 2145-2154

CODEN: GASTAB; ISSN: 0016-5085

PB Elsevier Inc.

DT Journal

LA English

AB Background & Aims: How specifically to treat pancreatic and other cancers harboring Fanconi anemia gene mutations has raised great interest recently, yet preclin. studies have been hampered by the lack of well-controlled human cancer models. Methods: We endogenously disrupted FANCC and FANCG in a human adenocarcinoma cell line and determined the impact of these genes on drug sensitivity, irradiation sensitivity, and genome maintenance. Results: FANCC and FANCG disruption abrogated FANCD2 monoubiquitination, confirming an impaired Fanconi anemia pathway function. On treatment with DNA interstrand-crosslinking agents, FANCC and FANCG disruption caused increased clastogenic damage, G2/M arrest, and decreased proliferation. The extent of hypersensitivity varied among agents, with ratios of inhibitory concentration 50% ranging from 2-fold for oxaliplatin to 14-fold for melphalan, a drug infrequently used in solid tumors. No hypersensitivity was observed on gemcitabine, etoposide, 3-aminobenzamide, NU1025, or hydrogen peroxide. FANCC and FANCG disruption also resulted in increased clastogenic damage on irradiation, but only FANCG disruption caused a subsequent decrease in relative survival. Finally, FANCC and FANCG disruption increased spontaneous chromosomal breakage, supporting the role of these genes in genome maintenance and likely explaining why they are mutated in sporadic cancer. Conclusions: Our human cancer cell model provides optimal controls to elucidate fundamental biol. features of individual Fanconi anemia gene defects and facilitates preclin. studies of therapeutic options. The impact of Fanconi gene defects on drug and irradiation sensitivity renders these genes promising targets for a specific, genotype-based therapy for individual cancer patients, providing a strong rationale for clin. trials.

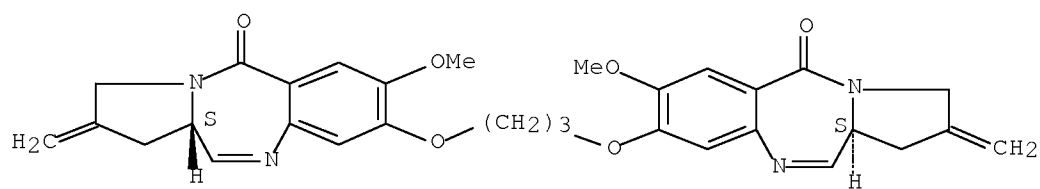
IT 232931-57-6, SJG-136

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(disruption of FANCC and FANCG genes increased sensitivity DNA interstrand-crosslinking agents like SJG-136 which induced chromosomal aberrations, cell cycle arrest and inhibited proliferation and survival of human adenocarcinoma cell)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



L18 ANSWER 20 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2006:696887 CAPLUS Full-text

DN 145:327689

TI Voltammetric studies of the interaction of pyrrolo[2,1-c][1,4]benzodiazepine (PBD) monomers and dimers with DNA

AU Marin, D.; Soler, L.; Thurston, D. E.

CS Departamento de Quimica Fisica, Facultad de Farmacia, Universidad de Alcala, Madrid, Alcala de Henares, 28871, Spain

SO Journal of Electroanalytical Chemistry (2006), 593(1-2), 241-246  
CODEN: JECHES

PB Elsevier B.V.

DT Journal

LA English

AB This study of the electrochem. activity of pyrrolo[2,1-c][1,4]benzodiazepine (PBD) mols. and their interaction with DNA extends previous similar studies on anthramycin by investigating a range of PBD monomers of various structures, and also the new PBD dimers which are shown here to be electroactive. A voltammetric study of seven pyrrolo[2,1-c][1,4]benzodiazepines, and the interaction of two examples of these with DNA in acetate buffer solution is described. Each of the PBDs studied was electroactive in acidic medium, providing a well-defined cathodic peak between -0.8 and -0.9 V and an anodic peak, which sometimes appeared as a shoulder, between -0.6 and -0.8 V. It was found that the PBDs adsorbed onto the electrode and that the electrode process was quasi-reversible. In general, adding DNA to a solution of a PBD decreased the  $I_p$  value of the cathodic and anodic peaks, and shifted  $E_p$  neg., consistent with decreasing concns. of the PBD. No new peaks appeared and no significant change in the electrochem. parameters of the PBDs was observed, suggesting that the PBD-DNA complex may either be non-electroactive or have a decreased transport rate to the electrode (i.e., a low  $D$  value) This work has established that, in principle, the electrochem. methodol. described here can be used to measure the kinetics of reaction of PBD mols. with DNA, and that the results are in accord with previously published studies using alternative techniques (e.g., UV spectroscopy). It is possible that the technique can be adapted in the future to measure the stoichiometry of PBD-DNA interaction.

IT 140676-21-7, DSB-120 232931-57-6, SJG-136

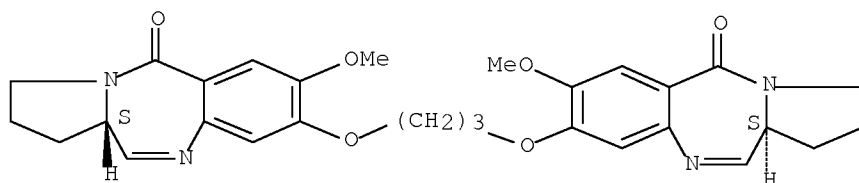
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)

(voltammetric studies of interaction of pyrrolobenzodiazepine monomers and dimers with DNA)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

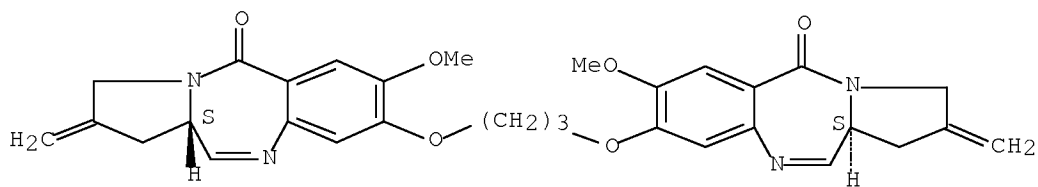


RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-,

(11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 21 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2006:642525 CAPLUS Full-text

DN 145:262666

TI Time-dependent cytotoxicity induced by SJG-136 (NSC 694501): influence of the rate of interstrand cross-link formation on DNA damage signaling

AU Arnould, Stephanie; Spanswick, Victoria J.; Macpherson, Janet S.; Hartley, John A.; Thurston, David E.; Jodrell, Duncan I.; Guichard, Sylvie M.

CS Pharmacology and Drug Development Group, Cancer Research UK Centre, The University of Edinburgh, Edinburgh, UK

SO Molecular Cancer Therapeutics (2006), 5(6), 1602-1609  
CODEN: MCTOCF; ISSN: 1535-7163

PB American Association for Cancer Research

DT Journal

LA English

AB SJG-136 is a new pyrrolobenzodiazepine dimer inducing time-dependent cytotoxicity. HCT 116 cells were exposed to 50 nmol/L of SJG-136 for 1 h or 1 nmol/L of SJG-136 for 24 h to achieve similar levels of interstrand cross-links (ICL). The short exposure led to a rapid formation of ICLs (1 h), early H2AX foci formation (4 h), prominent S phase arrest, and greater phosphorylation of Nbs1 (on serine 343) and Chk1 (on serine 317) than a 24-h exposure. The prolonged exposure at low concns. of SJG-136 induced a gradual formation of ICLs (up to 24 h) which was associated with a limited S phase arrest and delayed Nbs1 phosphorylation. Prolonged exposure was also associated with a reduced phosphorylation of p53 on serines 15 and 20, a limited and delayed phosphorylation on serine 392, and a less prominent increase in p21 levels. These data suggest that the 24-h exposure to a low concentration of SJG-136 led to delayed and reduced DNA damage signaling compared with a higher concentration of SJG-136 for 1 h, resulting in greater cytotoxicity and contributing to the time-dependent cytotoxic effect of SJG-136.

IT 232931-57-6, SJG-136

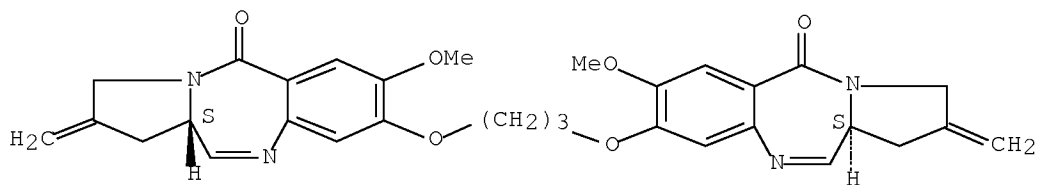
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(time-dependent cytotoxicity induced by SJG-136 influence of rate of interstrand cross-link formation on DNA damage signaling)

RN 232931-57-6 CAPLUS

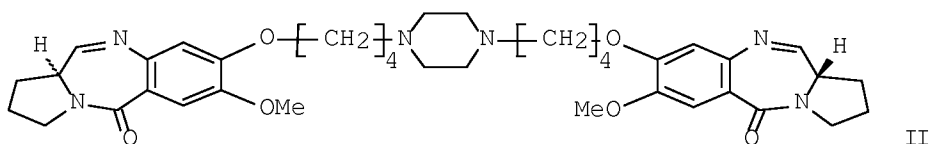
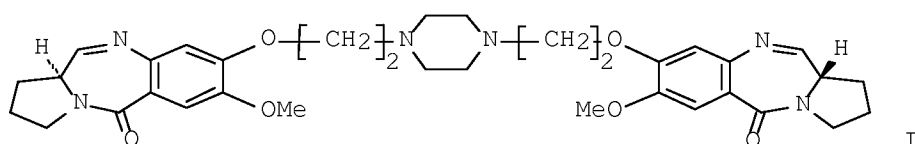
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 22 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:1301840 CAPLUS Full-text  
 DN 144:64035  
 TI DNA binding potential and cytotoxicity of newly designed  
 pyrrolobenzodiazepine dimers linked through a piperazine side-armed-alkane  
 spacer  
 AU Kamal, Ahmed; Reddy, P. S. Murali Mohan; Reddy, D. Rajasekhar; Laxman, E.  
 CS Biotransformation Laboratory, Division of Organic Chemistry, Indian  
 Institute of Chemical Technology, Hyderabad, 500 007, India  
 SO Bioorganic & Medicinal Chemistry (2006), 14(2), 385-394  
 CODEN: BMECEP; ISSN: 0968-0896  
 PB Elsevier B.V.  
 DT Journal  
 LA English  
 OS CASREACT 144:64035  
 GI



AB New pyrrolobenzodiazepine (PBD) dimers have been developed that are composed of two DC-81 subunits tethered to their C8 positions through piperazine moiety side-armed with alkaneoxy linkers (composed of 2-5 carbons). DNA thermal denaturation studies show that after 18 h of incubation with calf thymus DNA at a 1:5 ligand/DNA ratio, one of them (I) increases the  $\Delta T_m$  value by 24.0°. Thus, incorporation of a piperazine moiety instead of an inert alkanedioxy linker alone significantly enhances the DNA binding ability, and the analogous dimer that lacks a piperazine moiety in the linker spacer elevates melting by only 15.1° under identical exptl. conditions. This illustrates the effect of introducing a piperazine ring in the middle of such an alkanedioxy linker which produces several hydrophobic interactions and could also achieve a superior isohelical fit within the DNA minor groove. Interestingly, these dimers are significantly more cytotoxic than the dimer lacking a piperazine moiety in a number of human cancer cell lines, in particular, compound (II) is highly potent for almost all the nine human cancer cell lines.

IT 764680-79-7P 764680-84-4P 764680-89-9P  
 764680-91-3P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(DNA binding potential and cytotoxicity of newly designed  
 pyrrolobenzodiazepine dimers linked through a piperazine  
 side-armed-alkane spacer)

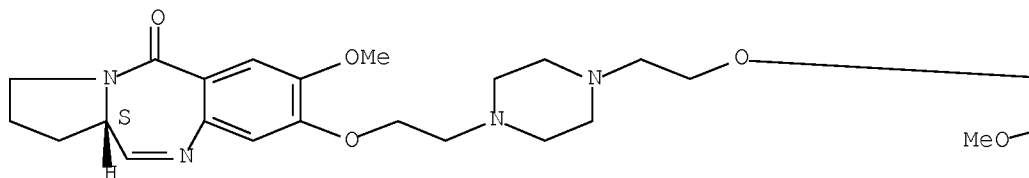
RN 764680-79-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-piperazinediylbis(2,1-

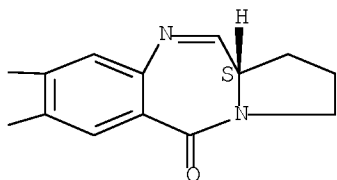
ethanediylloxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

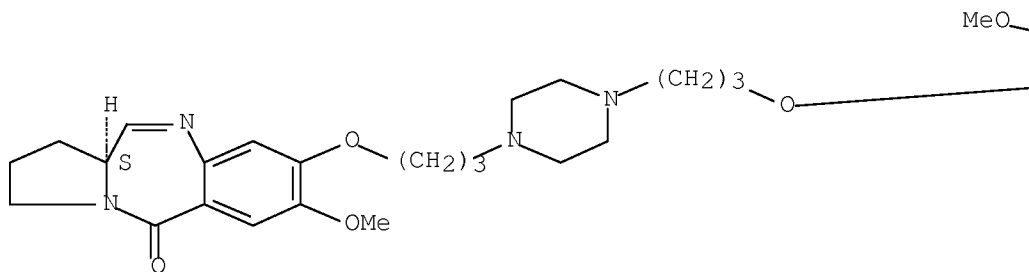


RN 764680-84-4 CAPLUS

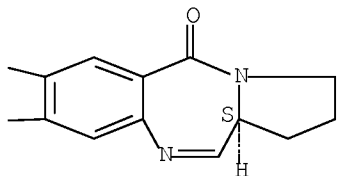
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-piperazinediylbis(3,1-propanediylloxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

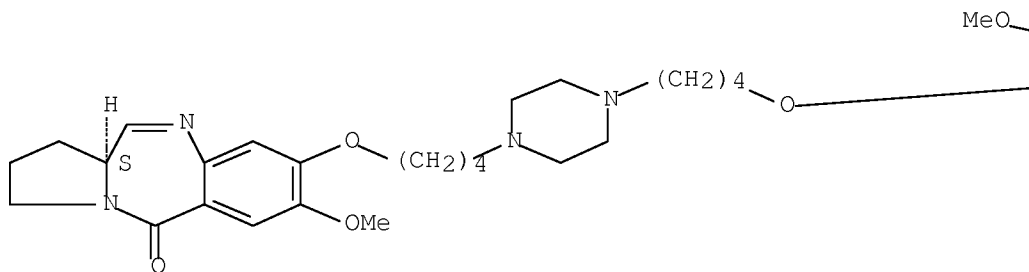


RN 764680-89-9 CAPLUS

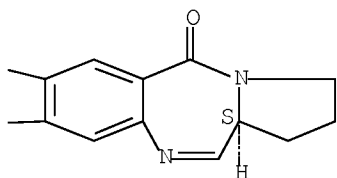
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-piperazinediylbis(4,1-butanediylloxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



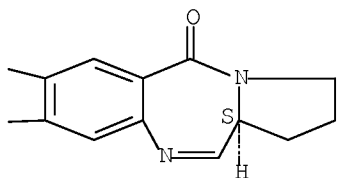
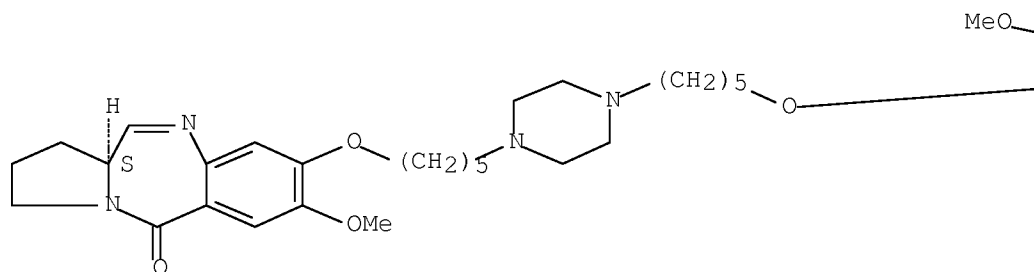
PAGE 1-B



RN 764680-91-3 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-piperazinediylbis(5,1-pentanediyloxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.



IT 140676-21-7, DSB-120

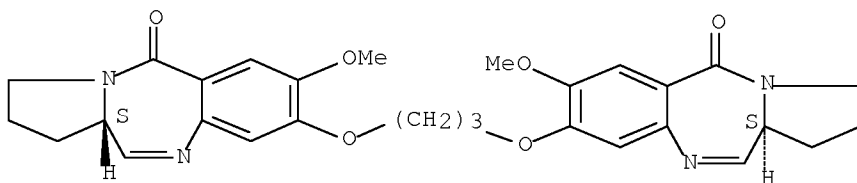
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)

(DNA binding potential and cytotoxicity of newly designed  
pyrrolobenzodiazepine dimers linked through a piperazine  
side-armed-alkane spacer)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
(CA INDEX NAME)

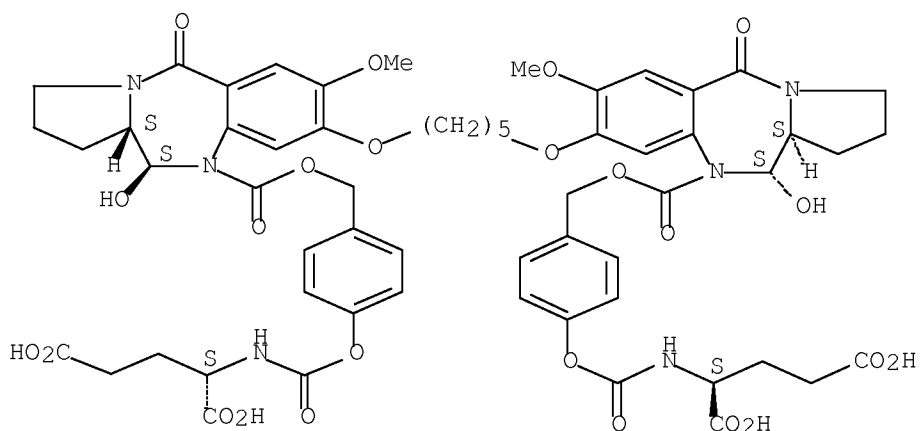
Absolute stereochemistry. Rotation (+).



RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



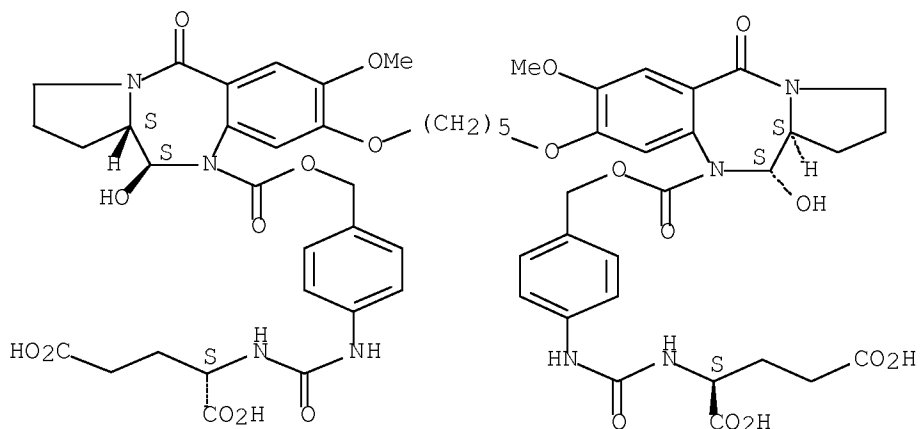




RN 848004-85-3 CAPLUS

CN L-Glutamic acid, N,N'-[1,5-pentanediy]bis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneiminocarbonyl]]bis- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 145325-57-1P

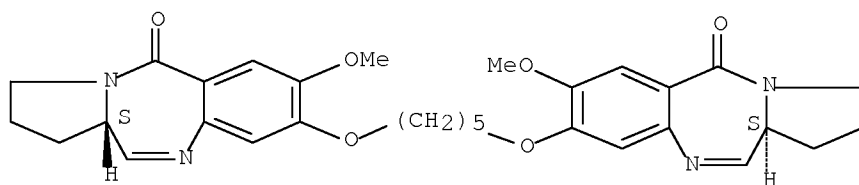
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(preparation and biol. evaluation of pyrrolo[2,1-c][1,4]benzodiazepine prodrugs for use in antibody-directed enzyme prodrug therapy)

RN 145325-57-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediy]bis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 24 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:1242440 CAPLUS Full-text

DN 143:472562

TI Antitumor Pyrrolobenzodiazepine for the treatment of Leukemia

IN Pepper, Christopher John; Thurston, David Edwin

PA Spirogen Limited, UK

SO PCT Int. Appl., 68 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 2005110423	A2	20051124	WO 2005-GB1881	20050513
	WO 2005110423	A3	20060119		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1755612	A2	20070228	EP 2005-744802	20050513
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
	US 20080090812	A1	20080417	US 2006-569007	20061113
PRAI	GB 2004-10725	A	20040513		
	WO 2005-GB1881	W	20050513		

OS MARPAT 143:472562

AB A pyrrolobenzodiazepine dimer compound, SJG-136 for the treatment of drug resistant leukemia is provided.

IT 232931-57-6P, SJG-136

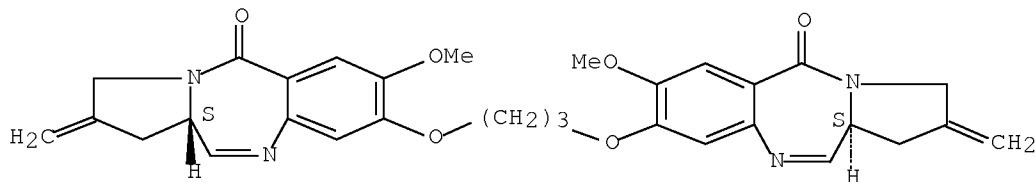
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(pyrrolobenzodiazepine therapeutic agents)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L18 ANSWER 25 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:1152782 CAPLUS Full-text  
 DN 143:399812  
 TI Therapeutic composition containing a pyrrolobenzodiazepine derivative and fludarabine  
 IN Delavault, Patrick  
 PA Societe de Conseils de Recherches et d'Applications Scientifiques SCRAS, Fr.  
 SO Fr. Demande, 12 pp.  
 CODEN: FRXXBL  
 DT Patent  
 LA French  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	FR 2869231	A1	20051028	FR 2004-4424	20040427
	FR 2869231	B1	20080314		
	CA 2564603	A1	20051110	CA 2005-2564603	20050426
	WO 2005105113	A2	20051110	WO 2005-FR1025	20050426
	WO 2005105113	A3	20070222		
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	RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	EP 1742644	A2	20070117	EP 2005-762344	20050426
	R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU			
	JP 2007534730	T	20071129	JP 2007-510074	20050426
	US 20070232592	A1	20071004	US 2006-587962	20061027
	NO 2006005368	A	20061121	NO 2006-5368	20061121
PRAI	FR 2004-4424	A	20040427		
	WO 2005-FR1025	W	20050426		

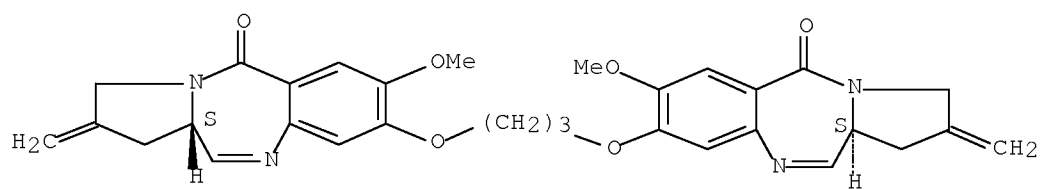
AB The use of a therapeutic composition comprising a derivative of the pyrrolobenzodiazepine in combination with fludarabine for the treatment of cancer, and more particularly, for hematol. diseases is disclosed. The pyrrolobenzodiazepine derivative is used at 1-150 µg/m2 (no data).

IT 232931-57-6  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (therapeutic composition containing pyrrolobenzodiazepine derivative and fludarabine)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 26 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:1078234 CAPLUS Full-text

DN 143:347210

TI A preparation of fluoropyrrolobenzodiazepine dimers, useful as antitumor agents

IN Kamal, Ahmed; Reddy, Peram Surakattula Murali Mohan; Reddy, Depatla Rajashekhar

PA Council of Scientific and Industrial Research, India

SO U.S. Pat. Appl. Publ., 13 pp.

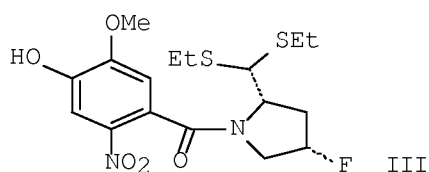
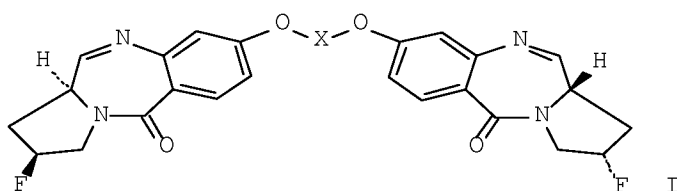
CODEN: USXXCO

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 20050222131	A1	20051006	US 2004-812840	20040330
	US 7189710	B2	20070313		
PRAI	US 2004-812840		20040330		
GI					



AB The invention relates to a preparation of fluoropyrrolobenzodiazepine dimers of formula I [wherein: X is (CH<sub>2</sub>)<sub>3-10</sub>], useful as antitumor agents. For instance, fluoropyrrolobenzodiazepine dimer II (I, X = (CH<sub>2</sub>)<sub>4</sub>; logGI<sub>50</sub> = -5.21, logTGI<sub>50</sub> = -4.75) was prepared from diethylthioacetal derivative III via 3 steps.

IT 717920-82-6P 717920-83-7P 717920-84-8P  
858639-17-5P 858639-19-7P 858639-21-1P  
858639-23-3P 858639-25-5P

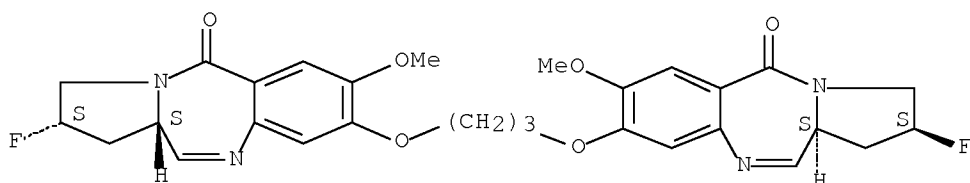
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of fluoropyrrolobenzodiazepine dimers useful as antitumor agents)

RN 717920-82-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

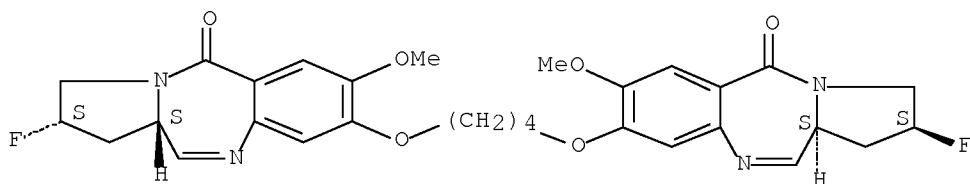
Absolute stereochemistry.



RN 717920-83-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

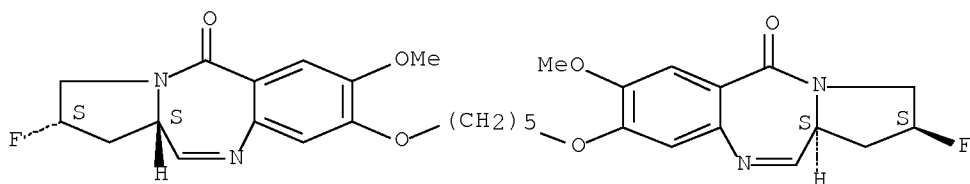
Absolute stereochemistry.



RN 717920-84-8 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediyibis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

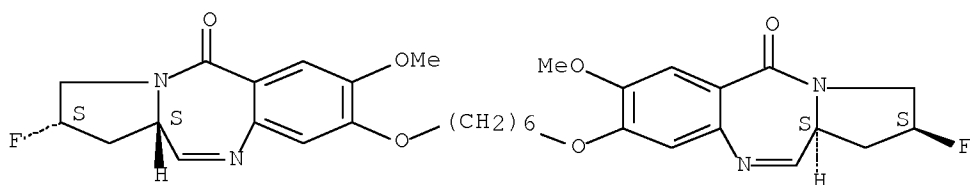
Absolute stereochemistry.



RN 858639-17-5 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,6-hexanediyibis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

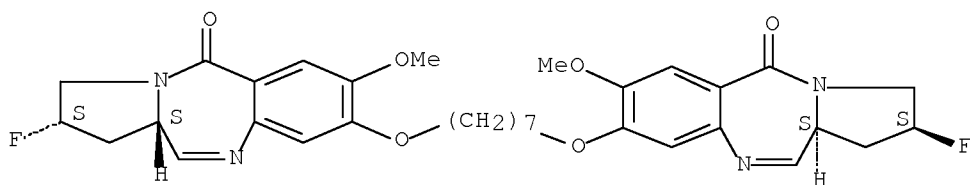
Absolute stereochemistry.



RN 858639-19-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,7-heptanediyibis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

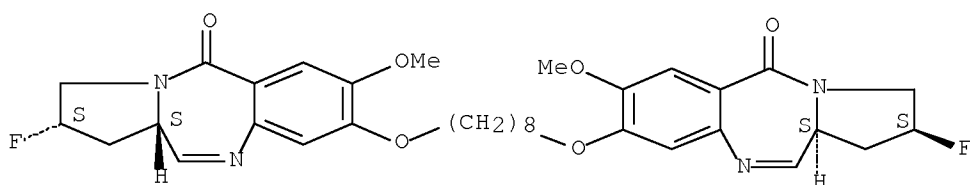
Absolute stereochemistry.



RN 858639-21-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,8-octanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

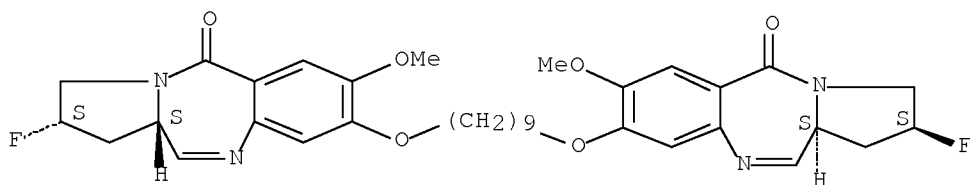
Absolute stereochemistry.



RN 858639-23-3 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,9-nonanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

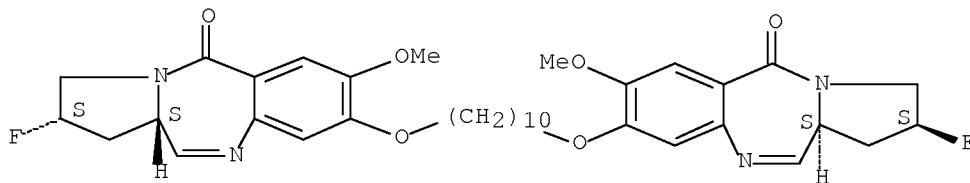
Absolute stereochemistry.



RN 858639-25-5 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,10-decanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



L18 ANSWER 27 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:1004755 CAPLUS Full-text

DN 143:306350

TI Preparation, DNA crosslinking reactivity, antitumor and antibacterial activity of pyrrolobenzodiazepine dimers

IN Howard, Philip Wilson; Gregson, Stephen John; Taylor, Peter William; Thurston, David Edwin; Hadjivassileva, Tsveta Stepanova

PA Spirogen Limited, UK

SO PCT Int. Appl., 62 pp.

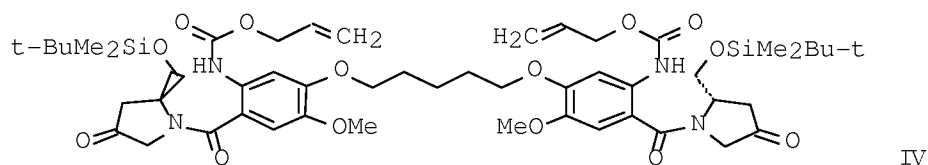
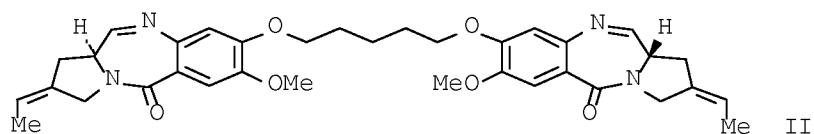
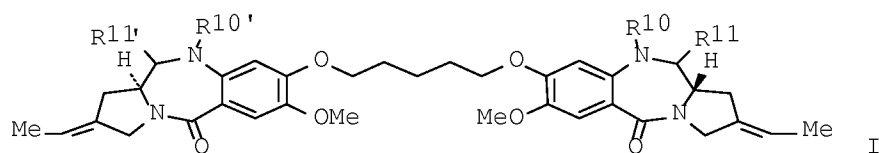
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005085260	A1	20050915	WO 2005-GB915	20050309
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
	RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	EP 1723152	A1	20061122	EP 2005-717979	20050309
	R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR			
	JP 2007528383	T	20071011	JP 2007-502398	20050309
	US 20070185073	A1	20070809	US 2007-598691	20070214
PRAI	GB 2004-5319	A	20040309		
	GB 2004-12409	A	20040603		
	WO 2005-GB915	W	20050309		
OS	CASREACT 143:306350; MARPAT 143:306350				
GI					



AB Title compds. I [R10 = N-protecting group; R11 = OH, OR12; R12 = O-protecting group; or R10 and R11 together form a double bond between N10 and C11; R10' = R10; R11' = R11; and their geometrical isomers, salts and solvates] were

prepared for use in the manufacture of a medicament for treating gene-based diseases, such as proliferative, and infections by Gram-pos. bacteria. For example, Z-, Z- isomer of II (III) was prepared, in 4 steps, by Wittig reaction of bis-ketone IV with ethyltriphenylphosphonium bromide, tert-butyltrimethylsilyl-deprotection, cyclization, and allyloxycarbonyl-deprotection. Pyrrolobenzodiazepine dimer III displayed antitumor potency (IC<sub>50</sub> 0.05 nM) against K562 human chronic myeloid leukemia cells and crosslinking reactivity (XL<sub>50</sub> = 2.7±1.6 nM). Pyrrolobenzodiazepine dimer III showed activity against Gram-pos. bacteria; for example the MIC<sub>90</sub> values for III were 0.03 against methicillin resistant Staphylococcus aureus, 0.06 mg/L against vancomycin resistant enterococci and Listeria monocytogenes, and 0.015 mg/L against Streptococcus pyogenes and Streptococcus agalactiae.

IT 864528-66-5P

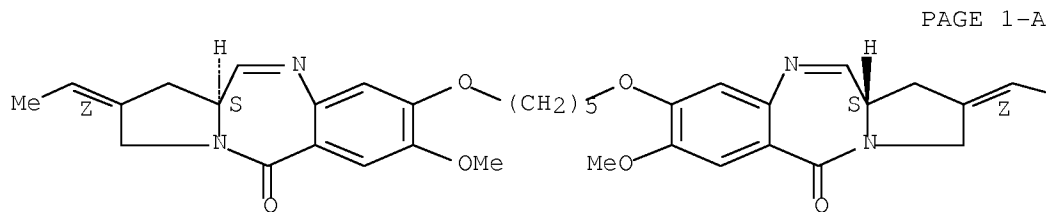
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrrolobenzodiazepine dimers as antiproliferative and antibacterial agents)

RN 864528-66-5 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediy]bis(oxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2Z,2'Z,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.



PAGE 1-B

— Me

IT 864528-73-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

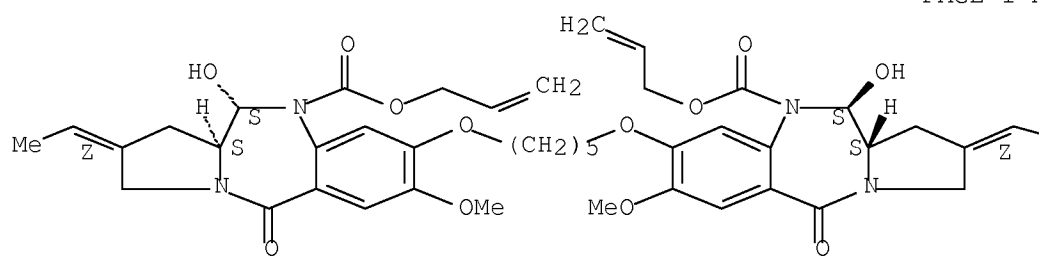
(intermediate; preparation of pyrrolobenzodiazepine dimers as antiproliferative and antibacterial agents)

RN 864528-73-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediy]bis(oxy)]bis[2-ethylidene-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, di-2-propenyl ester, (2Z,2'Z,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

Me

RE.CNT 9

THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 28 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:1004754 CAPLUS Full-text

DN 143:306349

TI Preparation, DNA crosslinking reactivity and antiproliferative activity of pyrrolobenzodiazepine dimers

IN Howard, Philip Wilson; Kang, Gyoung-Dong

PA Spirogen Limited, UK

SO PCT Int. Appl., 108 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 2005085259	A2	20050915	WO 2005-GB770	20050301
	WO 2005085259	A3	20060105		
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	RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	EP 1723151	A2	20061122	EP 2005-717848	20050301
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	IN 2006DN04922	A	20070817	IN 2006-DN4922	20060825
	US 20070191309	A1	20070816	US 2007-598482	20070206
PRAI	GB 2004-4577	A	20040301		
	WO 2005-GB770	W	20050301		
OS	CASREACT 143:306349; MARPAT 143:306349				
GI					

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Title compds. I [R2, R3 = independently H, :O, :CH2, CN, R, OR, halo, etc.; R6, R9 = independently H, R, OH, OR, NRR', SH, etc.; R, R' = independently (un)substituted alkyl, heterocyclyl, aryl; when X = RA, Y = OH or A-R''-A'-PDB; when X = OH or A-R''-A'-PDB, Y = RA; RA = H, R, OR, NO2, etc.; A, A' = independently O, S, NH; R'' = alkylene, optionally interrupted by one or more O, S, NH and/or aryl rings; PDB = pyrrolobenzodiazepine; R10 = carbamate-based N protecting group; R11 = O protecting group; or R10 and R11 together form a double bond between N10 and C11; and their salts, solvates, and chemical protected forms] were prepared for the manufacture of a medicament for treating a proliferative disease. Thus, reacting pyrrolobenzodiazepine (PBD) monomer II with 1,5-diiodopentane, followed by deprotection/dehydration gave PBD dimer III. PBD dimer III displayed antitumor potency (IC50 = 0.5 µM) against K562 human chronic myeloid leukemia cells DNA crosslinking reactivity (XL50 = 0.07 µM).

IT 140676-21-7P, (+)-1,1'-[(Propane-1,3-diyl)dioxy]bis[(11aS)-7-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
145325-56-0P, (+)-1,1'-[(Butane-1,4-diyl)dioxy]bis[(11aS)-7-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]

145325-57-1P, (+)-1,1'-[(Pentane-1,5-diyl)dioxy]bis[(11aS)-7-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 145325-58-2P, (+)-1,1'-[(Hexane-1,6-diyl)dioxy]bis[(11aS)-7-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-38-3P, (+)-1,1'-[(Propane-1,3-diyl)dioxy]bis[(11S,11aS)-8-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-40-7P, (+)-1,1'-[(Butane-1,4-diyl)dioxy]bis[(11aS)-8-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-42-9P, (+)-1,1'-[(Pentane-1,5-diyl)dioxy]bis[(11aS)-8-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-44-1P, (+)-1,1'-[(Hexane-1,6-diyl)dioxy]bis[(11aS)-8-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-46-3P, (+)-1,1'-[(Heptane-1,7-diyl)dioxy]bis[(11aS)-8-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-48-5P, (+)-1,1'-[(Octane-1,8-diyl)dioxy]bis[(11aS)-8-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-50-9P, (+)-1,1'-[(Nonane-1,9-diyl)dioxy]bis[(11aS)-8-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-52-1P, (+)-1,1'-[(Decane-1,10-diyl)dioxy]bis[(11aS)-8-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-54-3P, (+)-1,1'-[(Undecane-1,1-diyl)dioxy]bis[(11aS)-8-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-56-5P, (+)-1,1'-[(Dodecane-1,12-diyl)dioxy]bis[(11aS)-8-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-66-7P, (+)-1,1'-[(Heptane-1,7-diyl)dioxy]bis[(11aS)-7-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-68-9P, (+)-1,1'-[(Octane-1,8-diyl)dioxy]bis[(11aS)-7-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-70-3P, (+)-1,1'-[(Nonane-1,9-diyl)dioxy]bis[(11aS)-7-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-72-5P, (+)-1,1'-[(Decane-1,10-diyl)dioxy]bis[(11aS)-7-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-74-7P, (+)-1,1'-[(Undecane-1,1-diyl)dioxy]bis[(11aS)-7-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-75-8P 864665-76-9P, (+)-1,1'-[(Dodecane-1,12-diyl)dioxy]bis[(11aS)-7-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one] 864665-86-1P, (+)-1,1'-[(Octane-1,8-diyl)dioxy]bis[(11aS)-7-methoxy-2-methylene-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one] 864665-88-3P, (+)-1,1'-[(Nonane-1,9-diyl)dioxy]bis[(11aS)-7-methoxy-2-methylene-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]  
 864665-90-7P, (+)-1,1'-[(Decane-1,10-diyl)dioxy]bis[(11aS)-7-methoxy-2-methylene-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one]

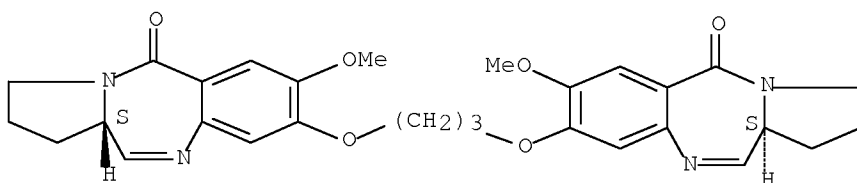
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation, DNA crosslinking reactivity and cytotoxicity of pyrrolobenzodiazepines)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

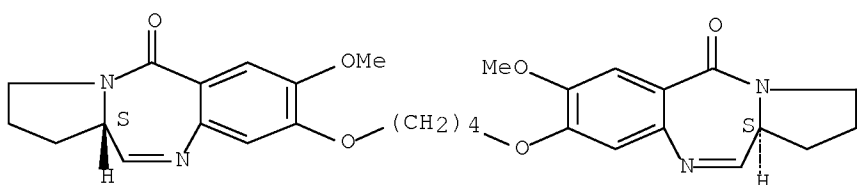
Absolute stereochemistry. Rotation (+).



RN 145325-56-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

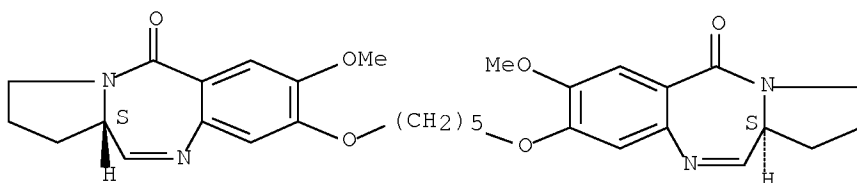
Absolute stereochemistry.



RN 145325-57-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanedylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

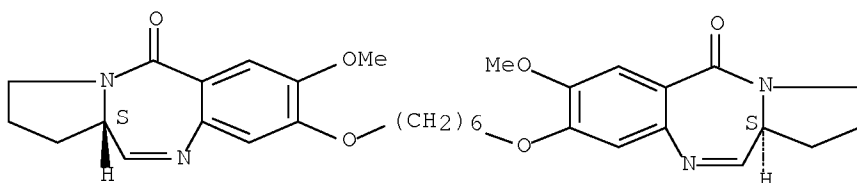
Absolute stereochemistry. Rotation (+).



RN 145325-58-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,6-hexanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

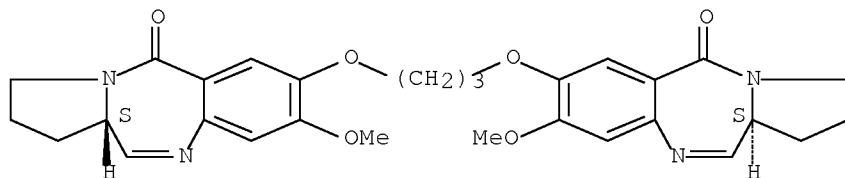
Absolute stereochemistry. Rotation (+).



RN 864665-38-3 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-8-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

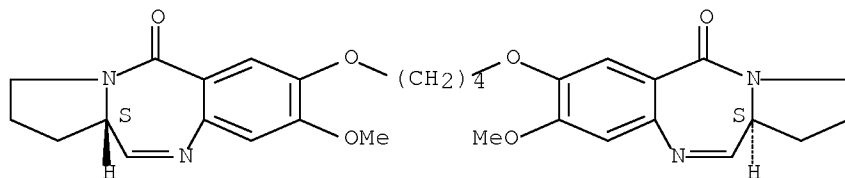
Absolute stereochemistry. Rotation (+).



RN 864665-40-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-8-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

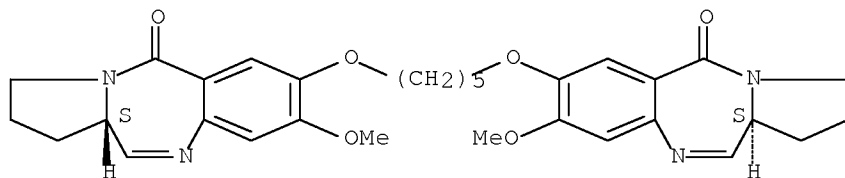
Absolute stereochemistry. Rotation (+).



RN 864665-42-9 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[1,5-pentanediybis(oxy)]bis[1,2,3,11a-tetrahydro-8-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

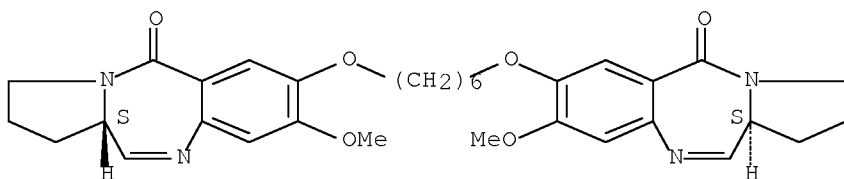
Absolute stereochemistry. Rotation (+).



RN 864665-44-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[1,6-hexanediybis(oxy)]bis[1,2,3,11a-tetrahydro-8-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

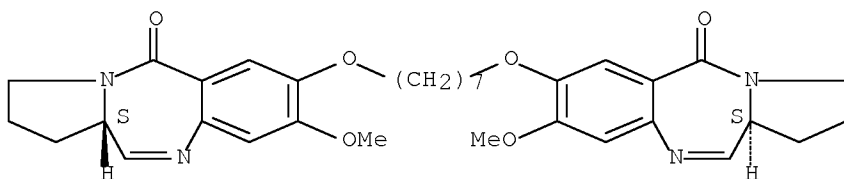
Absolute stereochemistry. Rotation (+).



RN 864665-46-3 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[1,7-heptanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-8-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

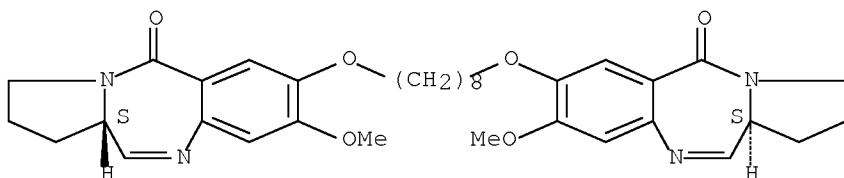
Absolute stereochemistry. Rotation (+).



RN 864665-48-5 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[1,8-octanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-8-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

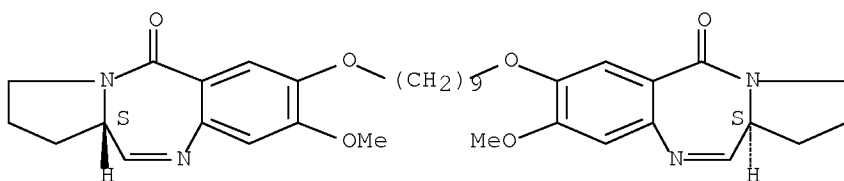


RN 864665-50-9 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[1,9-nonanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-8-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

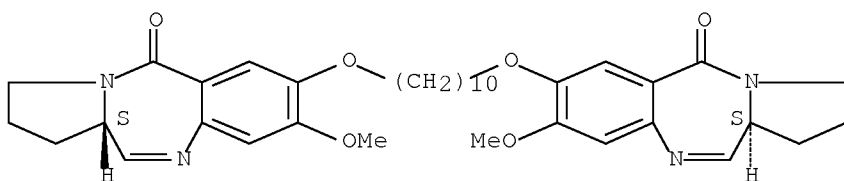




RN 864665-52-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[1,10-decanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-8-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

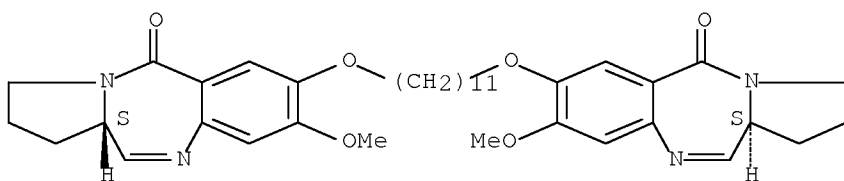
Absolute stereochemistry. Rotation (+).



RN 864665-54-3 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[1,11-undecanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-8-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

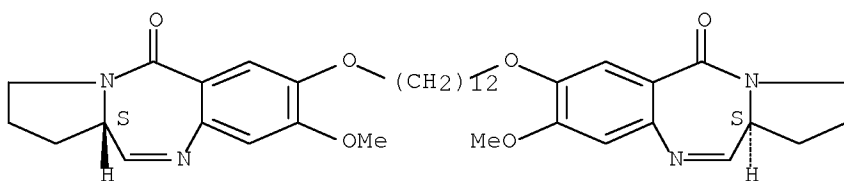
Absolute stereochemistry. Rotation (+).



RN 864665-56-5 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[1,12-dodecanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-8-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

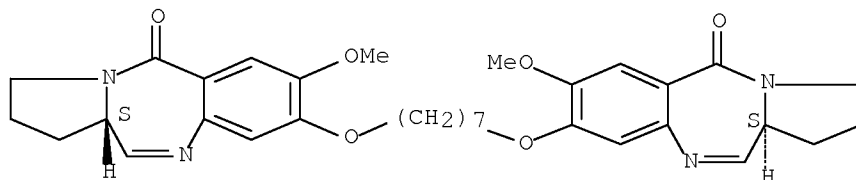
Absolute stereochemistry. Rotation (+).



RN 864665-66-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,7-heptanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

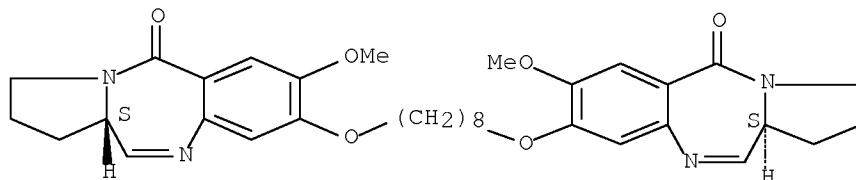
Absolute stereochemistry. Rotation (+).



RN 864665-68-9 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,8-octanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

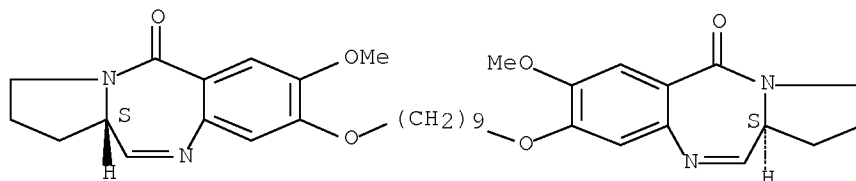
Absolute stereochemistry. Rotation (+).



RN 864665-70-3 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,9-nonanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

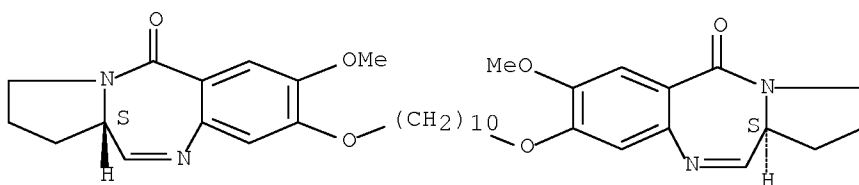
Absolute stereochemistry.



RN 864665-72-5 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,10-decanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

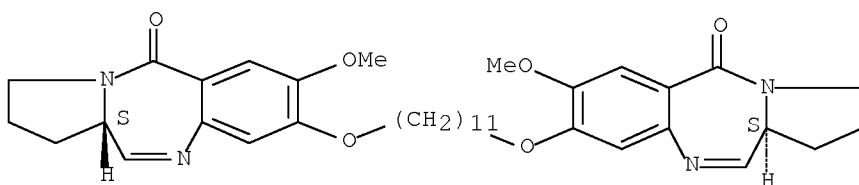
Absolute stereochemistry. Rotation (+).



RN 864665-74-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,11-undecanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

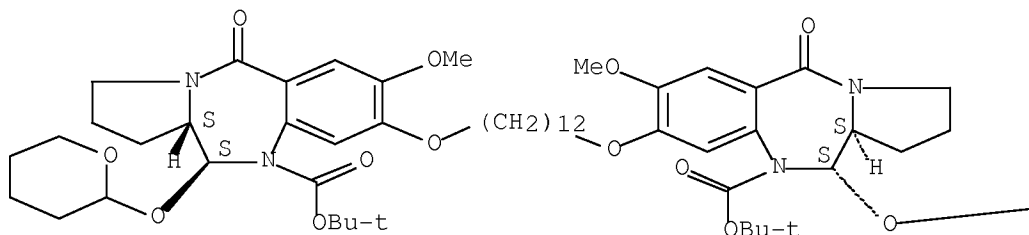
Absolute stereochemistry. Rotation (+).



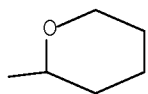
RN 864665-75-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,12-dodecanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

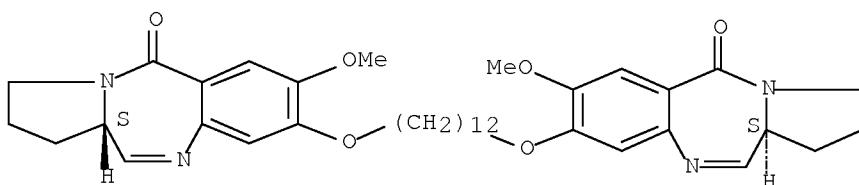


PAGE 1-A



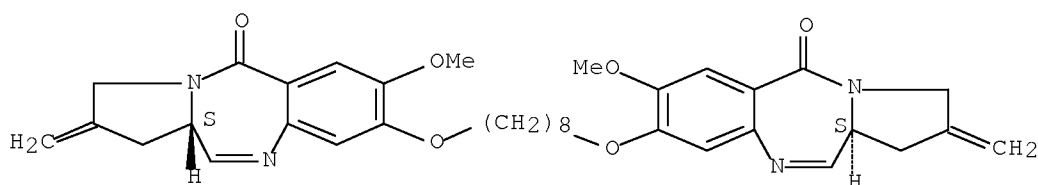
RN 864665-76-9 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,12-dodecanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



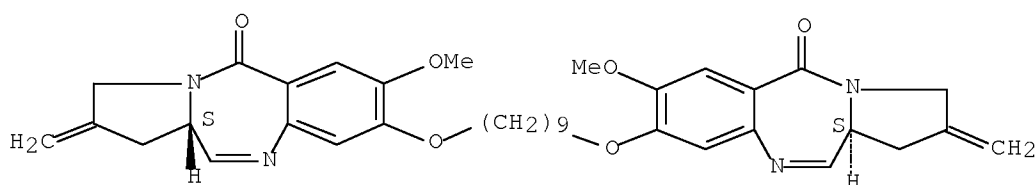
RN 864665-86-1 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,8-octanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 864665-88-3 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,11-undecanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

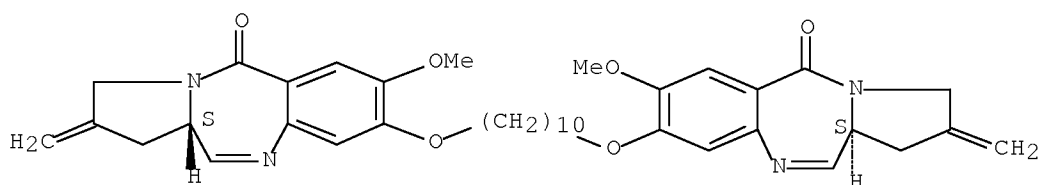
Absolute stereochemistry. Rotation (+).



RN 864665-90-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,10-decanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 864665-37-2P 864665-39-4P 864665-41-8P  
 864665-43-0P 864665-45-2P 864665-47-4P  
 864665-49-6P 864665-51-0P 864665-53-2P  
 864665-55-4P 864665-61-2P 864665-62-3P  
 864665-63-4P 864665-64-5P 864665-65-6P  
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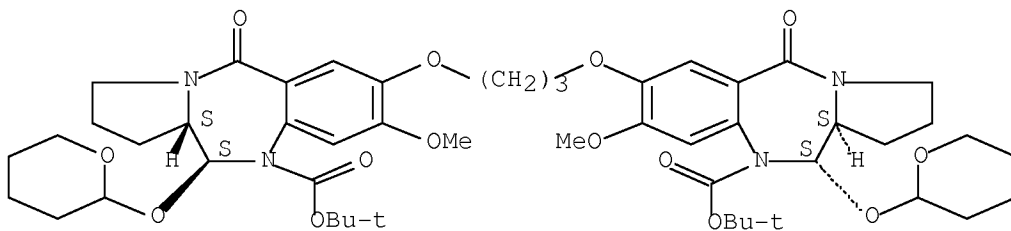
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation, DNA crosslinking reactivity and cytotoxicity of pyrrolobenzodiazepines)

RN 864665-37-2 CAPLUS

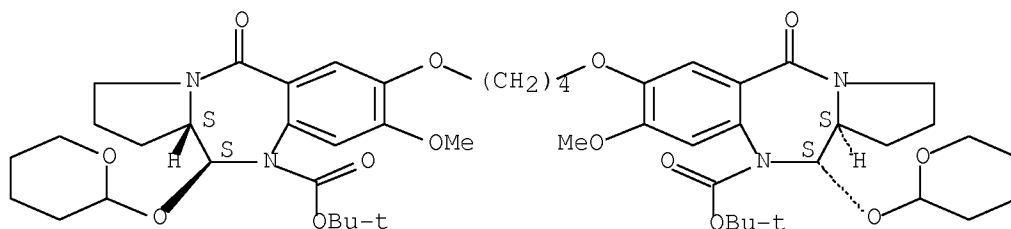
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 7,7'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



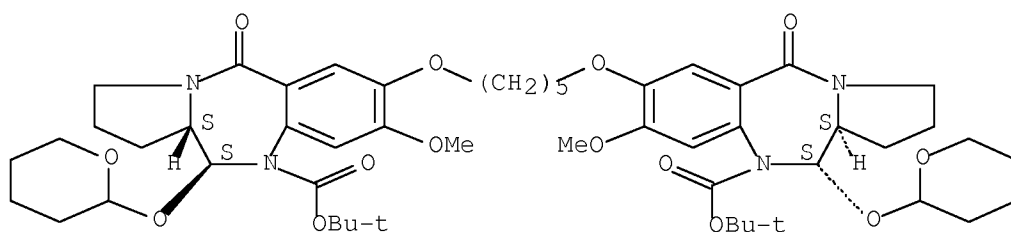
RN 864665-39-4 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,4-butanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



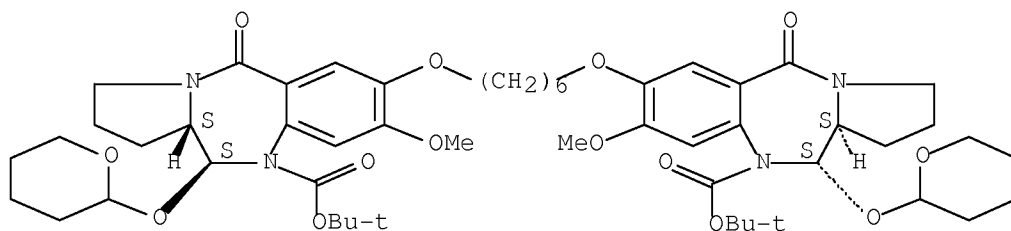
RN 864665-41-8 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,5-pentanediybis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 864665-43-0 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,6-hexanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

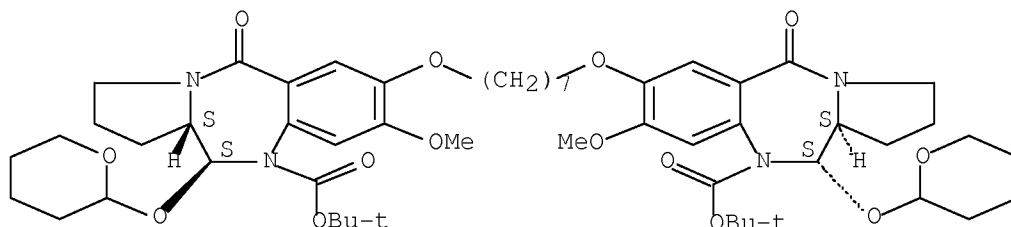
Absolute stereochemistry.



RN 864665-45-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,7-heptanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

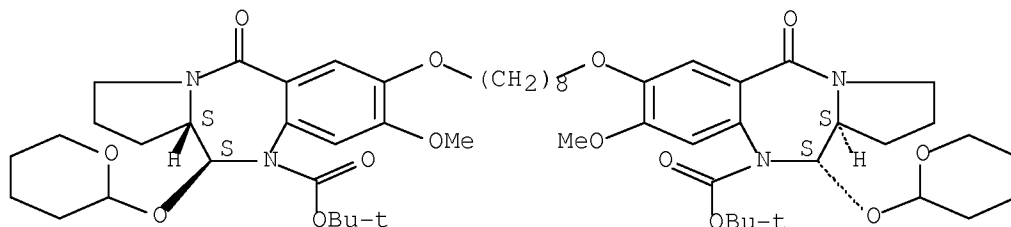
Absolute stereochemistry.



RN 864665-47-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,8-octanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

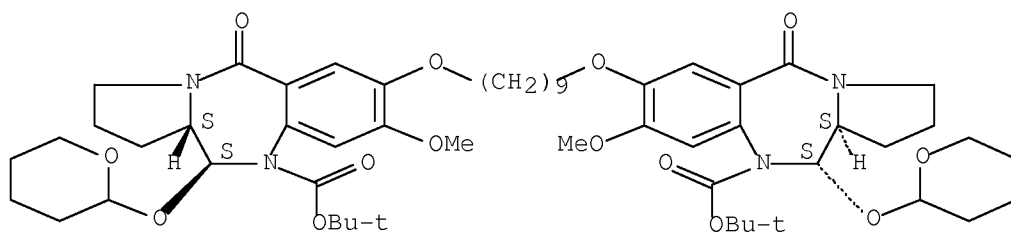
Absolute stereochemistry.



RN 864665-49-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,9-nonanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

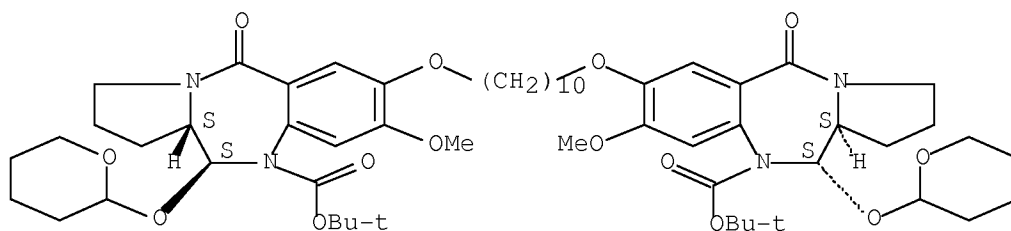
Absolute stereochemistry.



RN 864665-51-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,10-decanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

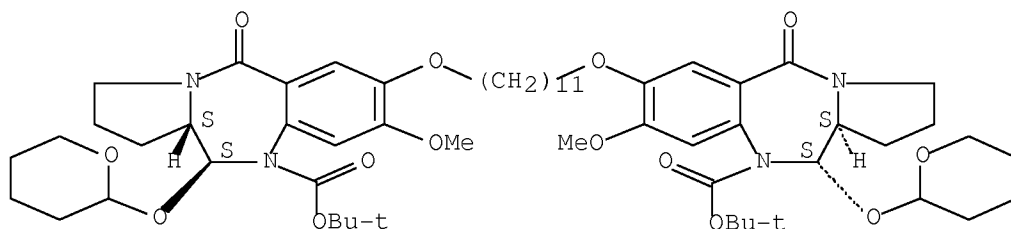
Absolute stereochemistry.



RN 864665-53-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,11-undecanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-  
11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

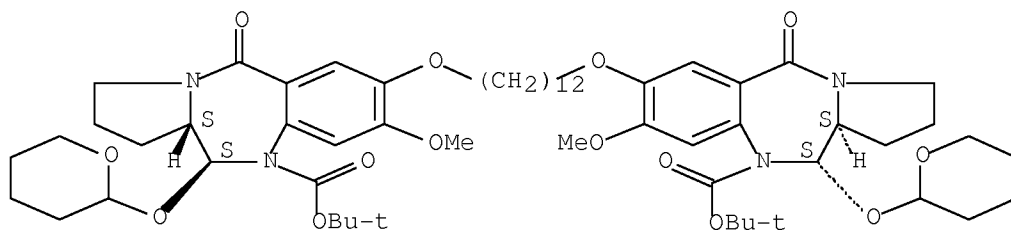


RN 864665-55-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
7,7'-[1,12-dodecanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-  
11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)



Absolute stereochemistry.

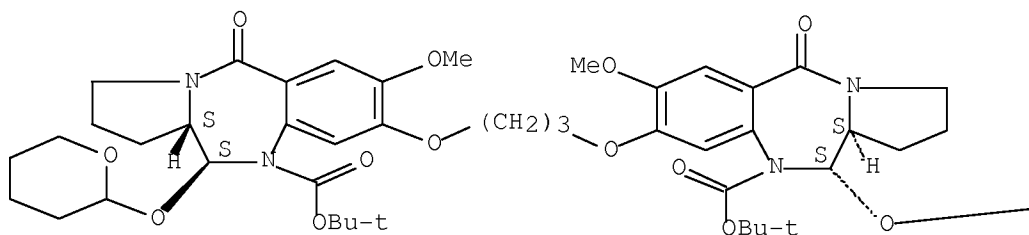


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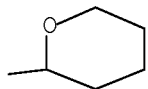
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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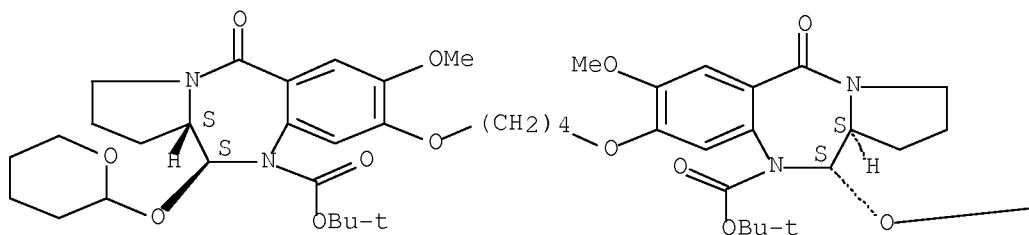


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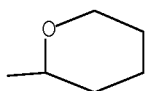
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,4-butanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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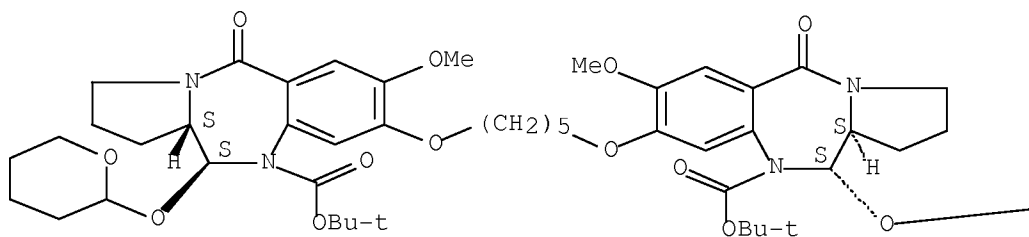
PAGE 1-B



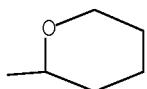
RN 864665-63-4 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,5-pentanediylobis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
 [(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
 (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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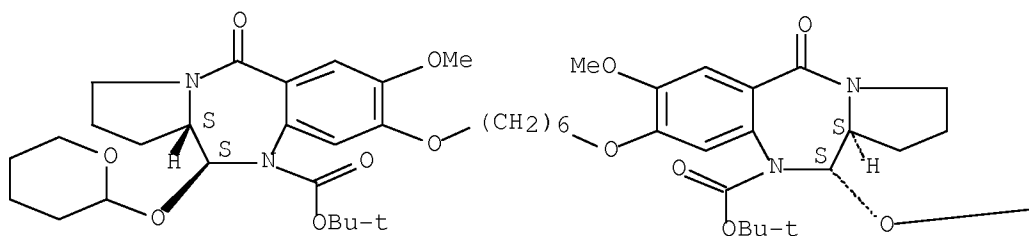


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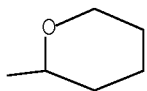
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,6-hexanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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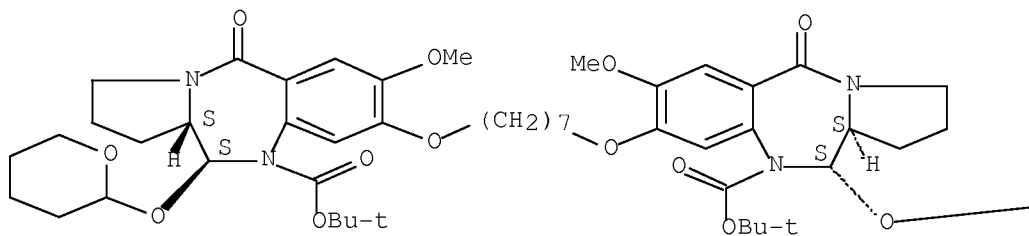


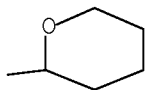
RN 864665-65-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,7-heptanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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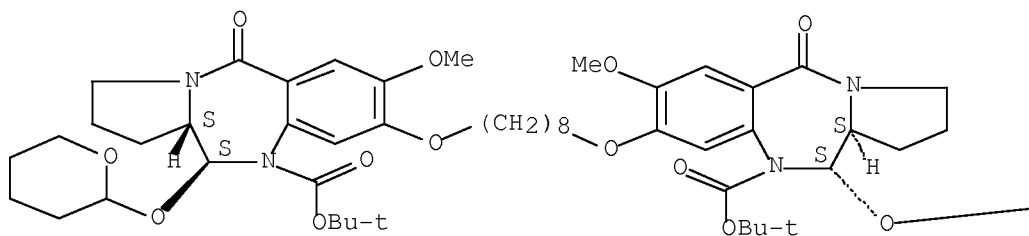


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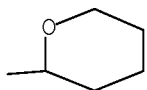
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,8-octanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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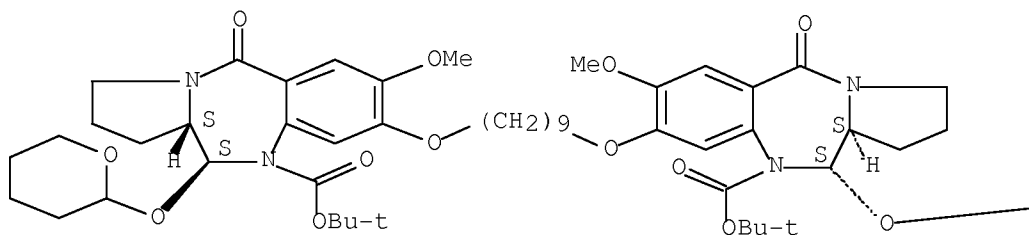


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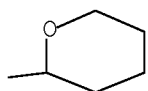
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,9-nonanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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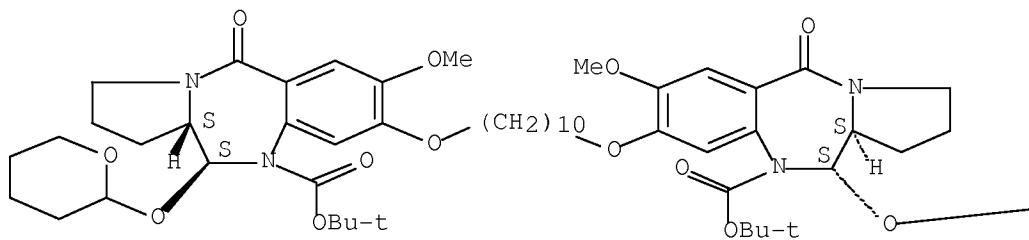
PAGE 1-B



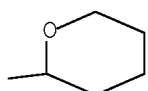
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 8,8'-[1,10-decanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
 [(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
 (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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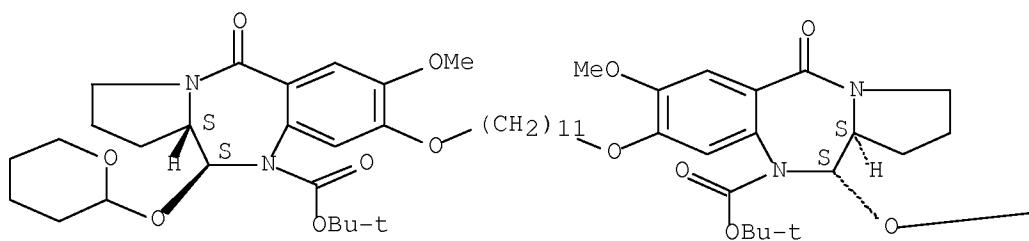
PAGE 1-B



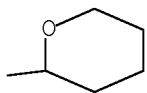
RN 864665-73-6 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,11-undecanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-  
 11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,  
 (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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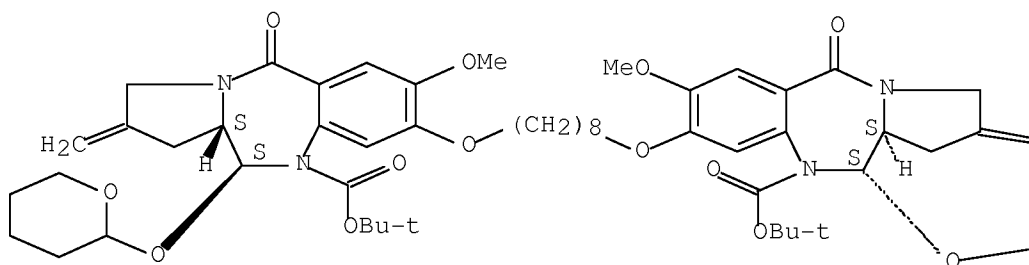
PAGE 1-B

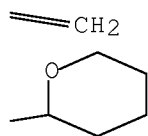


RN 864665-85-0 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,8-octanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-2-  
 methylene-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-  
 dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

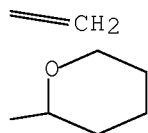
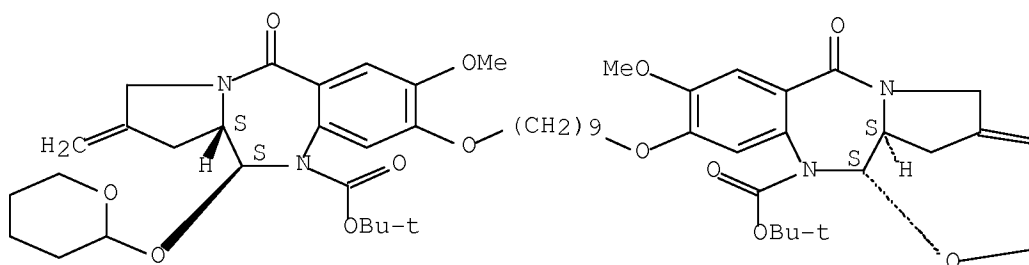
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RN 864665-87-2 CAPLUS  
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 8,8'-[1,9-undecanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-2-  
 methylene-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-  
 dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

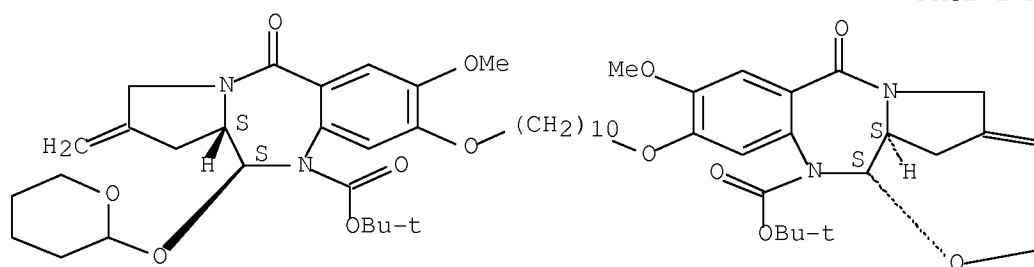


RN 864665-89-4 CAPLUS  
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 8,8'-[1,10-decanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-2-  
 methylene-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-

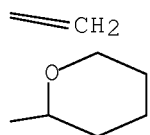
dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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L18 ANSWER 29 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:1004748 CAPLUS Full-text

DN 143:306348

TI Preparation of pyrrolobenzodiazepinone derivatives as antitumor agents

IN Howard, Philip Wilson; Gregson, Stephen John

PA Spirogen Limited, UK

SO PCT Int. Appl., 88 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PRAI	GB 2004-4575	A	20040301		
	GB 2004-26392	A	20041201		
	WO 2005-GB768	W	20050301		
OS	CASREACT 143:306348; MARPAT 143:306348				
GI					

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Title compds. I [R1 = labile leaving group, alkenyl or substituted phenyl; R2 and R5 independently = H, OH, SH, etc.; R3 and R4 independently = H, NH2, halo, etc. or the compound is a dimer with each monomer being of formula I, where the R3 and R4 groups of each monomer form together a dimer bridge -X-R-X-; R = alkylene group, which may be interrupted by heteroatoms or aromatic rings; X = O, S or NH; R6 = carbamate-based N-protecting group; R7 = oxygen protecting group or OH or R6 and R7 together form double bond between N10 and C11] and their pharmaceutically acceptable salts, are prepared and disclosed as antitumor agents. Thus, e.g., II was prepared by palladium catalyzed coupling of III (preparation given) with trans-propenylboronic acid followed by deprotection. The in vitro cytotoxicity of I towards K562 human chronic myeloid leukemia cells was evaluated using ELISA assay and it was revealed that selected compds. of the invention displayed IC50 values of less than 1  $\mu$ M. I should prove useful in the treatment of proliferative diseases such as leukemia. Pharmaceutical compns. comprising I are disclosed.

IT 864754-61-0P 864754-63-2P 864754-66-5P

864754-70-1P 864754-72-3P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP

(Preparation); RACT (Reactant or reagent); USES (Uses)

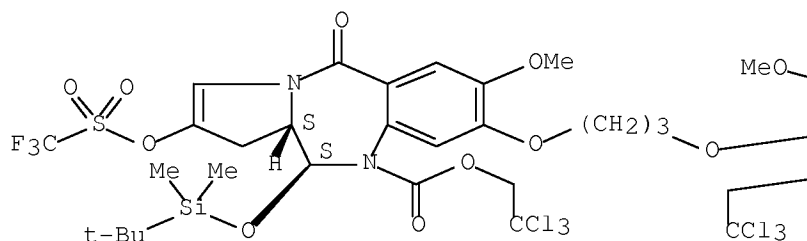
(preparation of pyrrolobenzodiazepinone derivs. as antitumor agents)

RN 864754-61-0 CAPLUS

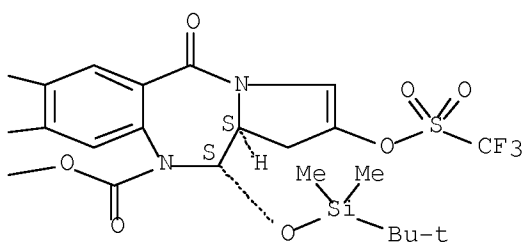
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[11-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-11,11a-dihydro-7-methoxy-5-oxo-2-[[[(trifluoromethyl)sulfonyl]oxy]-, bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



PAGE 1-B



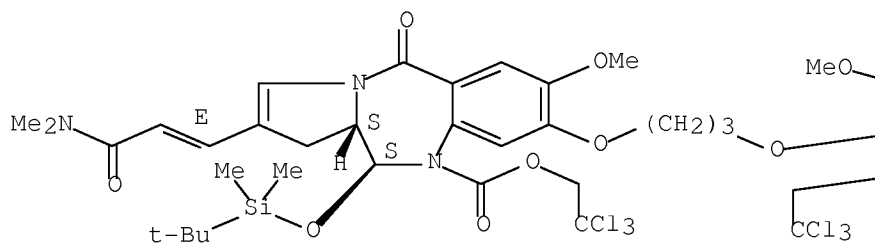
RN 864754-63-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2-[(1E)-3-(dimethylamino)-3-oxo-1-propenyl]-11-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-11,11a-dihydro-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

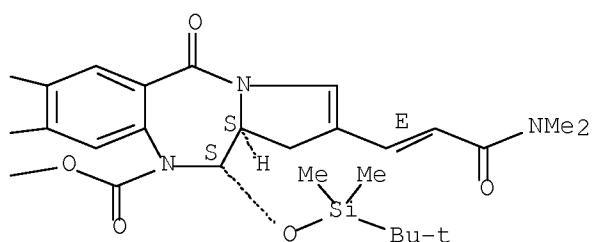
Absolute stereochemistry. Rotation (+).

Double bond geometry as shown.

PAGE 1-A



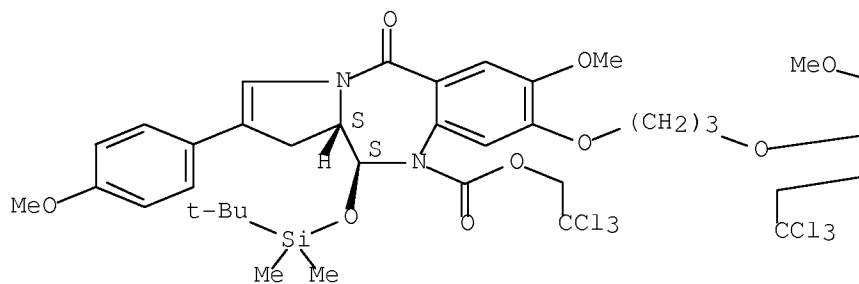
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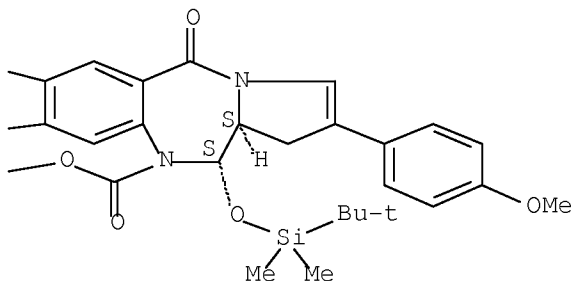


RN 864754-66-5 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl]dimethylsilyl]ox  
 y]-11,11a-dihydro-7-methoxy-2-(4-methoxyphenyl)-5-oxo-,  
 bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
 NAME)

Absolute stereochemistry.

PAGE 1-A

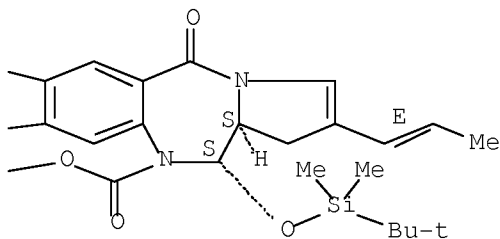
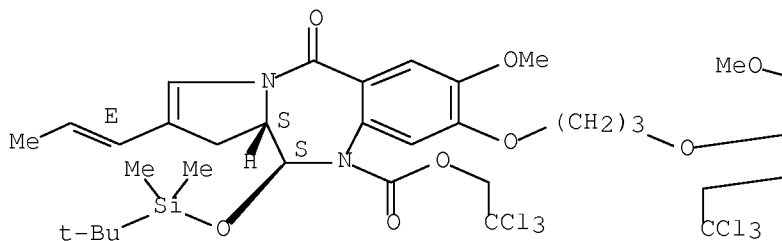




RN 864754-70-1 CAPLUS

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8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]ox  
y]-11,11a-dihydro-7-methoxy-5-oxo-2-(1E)-1-propenyl-, bis(2,2,2-  
trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.

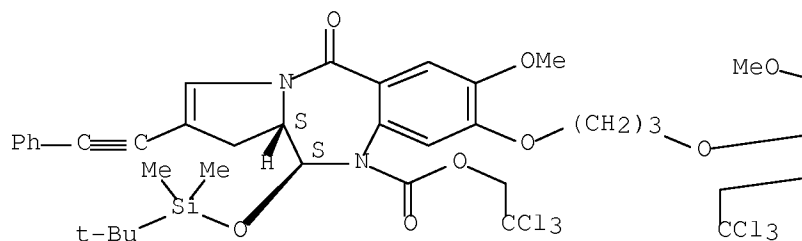


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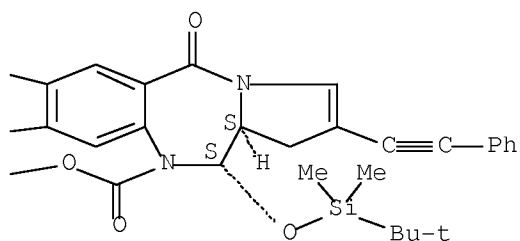
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]ox  
y]-11,11a-dihydro-7-methoxy-5-oxo-2-(phenylethynyl)-, bis(2,2,2-  
trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



IT 864754-65-4P 864754-68-7P 864754-71-2P  
864754-73-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
(Uses)

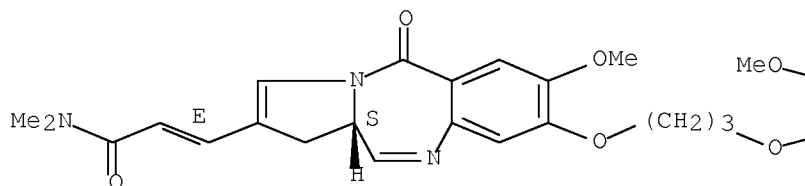
(preparation of pyrrolobenzodiazepinone derivs. as antitumor agents)

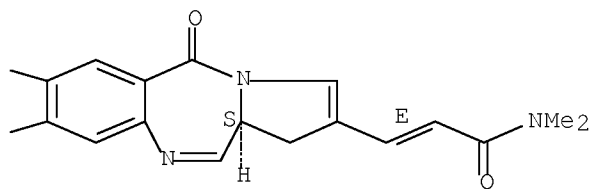
RN 864754-65-4 CAPLUS

CN 2-Propenamide, 3,3'-[1,3-propanediylbis[oxy[(11aS)-5,11a-dihydro-7-methoxy-  
5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,2-diyl]]]bis[N,N-dimethyl-,  
(2E,2'E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.

PAGE 1-A

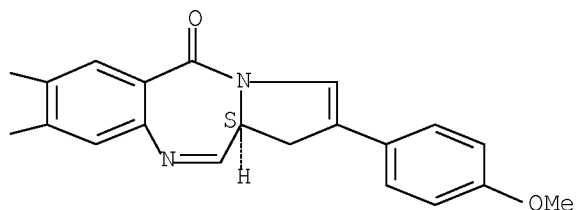
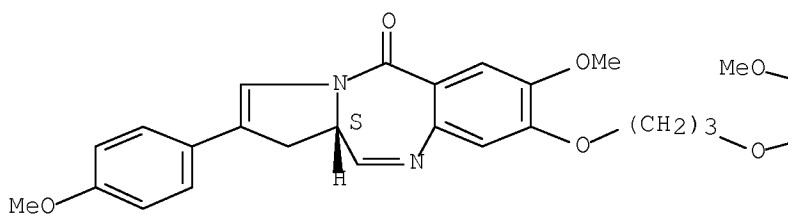




RN 864754-68-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,11a-dihydro-7-methoxy-2-(4-methoxyphenyl)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



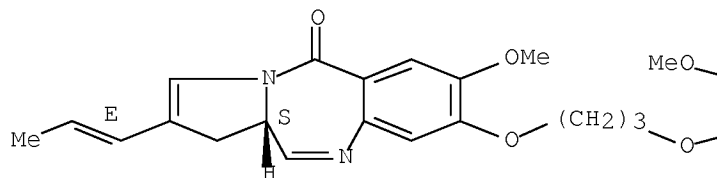
RN 864754-71-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,11a-dihydro-7-methoxy-2-(1E)-1-propenyl-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

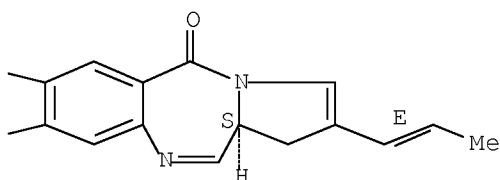
Absolute stereochemistry. Rotation (+).

Double bond geometry as shown.

PAGE 1-A



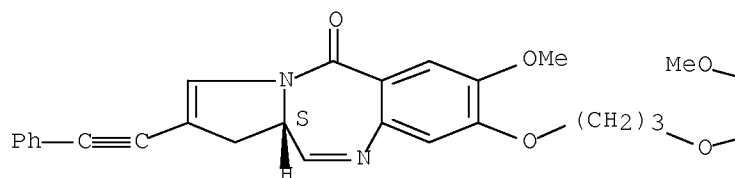
PAGE 1-B



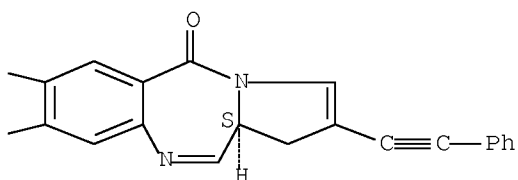
RN 864754-73-4 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,11a-dihydro-7-methoxy-2-(phenylethynyl)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



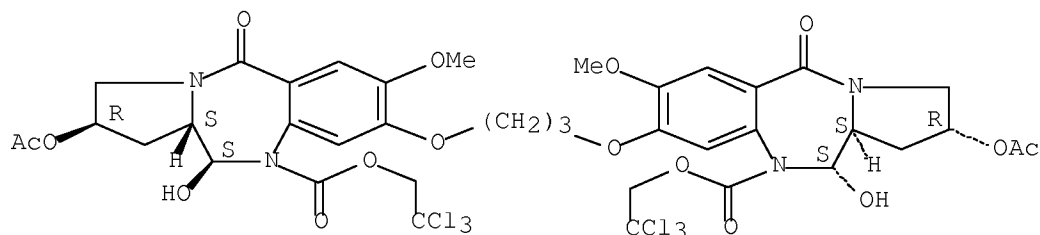
PAGE 1-B



IT 864755-08-8P 864755-09-9P 864755-10-2P  
 864755-11-3P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (preparation of pyrrolobenzodiazepinone derivs. as antitumor agents)

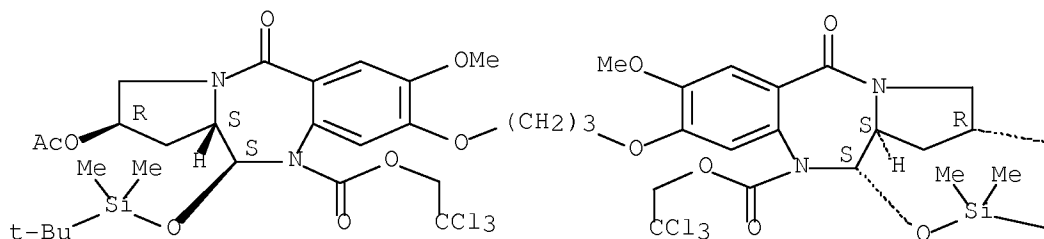
RN 864755-08-8 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[2-(acetyloxy)-2,3,11,11a-tetrahydro-11-  
 hydroxy-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester,  
 (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 864755-09-9 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[2-(acetyloxy)-11-[[1,1-  
 dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-,  
 bis(2,2,2-trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA  
 INDEX NAME)

Absolute stereochemistry.



PAGE 1-A

PAGE 1-B

--- OAc

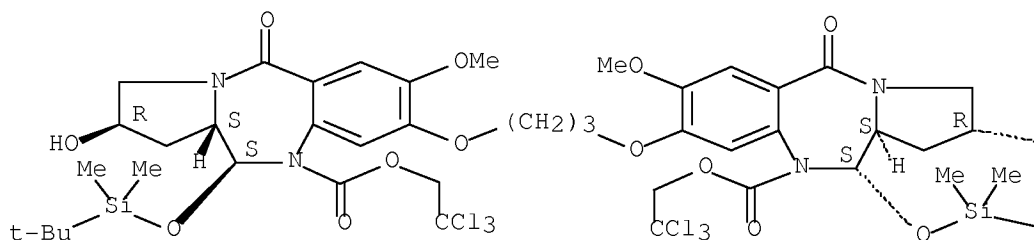
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RN 864755-10-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]ox  
 y]-2,3,11,11a-tetrahydro-2-hydroxy-7-methoxy-5-oxo-, bis(2,2,2-  
 trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX  
 NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

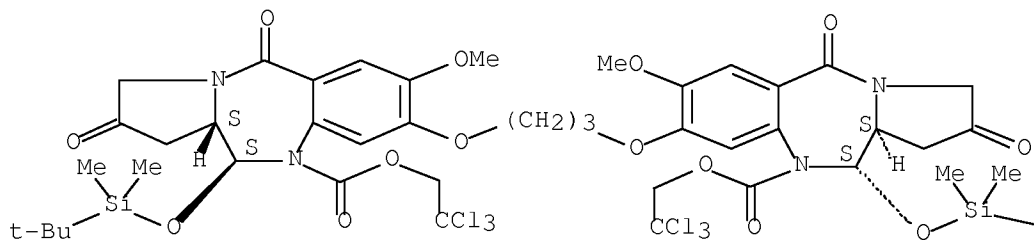
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---Bu-t

RN 864755-11-3 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[1,1-dimethylethyl)dimethylsilyl]ox  
 y]-2,3,11,11a-tetrahydro-7-methoxy-2,5-dioxo-, bis(2,2,2-trichloroethyl)  
 ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

— Bu-t

RE.CNT 10      THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 30 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:1004747 CAPLUS Full-text  
 DN 143:306347  
 TI Preparation of C8/C8' linked 5-oxo-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c]-  
 1,4-benzodiazepine dimers with 1H-pyrrole-dicarboxylic acid amide linkers  
 and oligomeric analogs thereof as well as related compounds for the  
 treatment of proliferative diseases  
 IN Howard, Philip Wilson; Gregson, Stephen John; Tiberghien, Arnaud Charles  
 PA Spirogen Limited, UK  
 SO PCT Int. Appl., 108 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

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PRAI	GB 2004-4578	A	20040301		
	WO 2005-GB767	W	20050301		
OS	CASREACT 143:306347; MARPAT 143:306347				
GI					

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Title compds. I [Z = AYX(Het)naL(Het)nbL(Het)ncT(Het')ndL(Het')neL(Het')nf  
 X'Y'A'; A = O, S, NH, or bond; Y = divalent group or single bond; X and X' are  
 both either NH or CO; Het and Het' independently = aminoheteroarylenecarbonyl;  
 each L independently =  $\beta$ -alanine, glycine, 4-aminobutanoic acid or single  
 bond; T = divalent linker group; A', Y' are independently selected definitions  
 for A and Y; na, mb, mc, nd, ne, nf independently = 0-5 with their sum = 0-16;  
 R2 and R3 = H, OH, CN, etc.; R6, R7 and R9 independently = H, SH, NH<sub>2</sub>, NO<sub>2</sub>,  
 etc.; R10 = N-protecting group; R15 = OH, =O, =S, OR where R = protecting  
 group; R10 and R15 may together form a double bond between atoms to which they  
 are attached], and their pharmaceutically acceptable salts, are prepared and  
 disclosed as antiproliferative agents. Thus, e.g., II was prepared by  
 bischlorination of N-methyl-2,5-pyrroledicarboxylic acid followed by  
 bisamidation with aniline III and removal of N-protecting group. I were  
 evaluated for DNA crosslinking ability, in vitro cytotoxicity in human chronic  
 myeloid leukemia cells and screened against 60 human tumor cell lines. For  
 example, compound II demon stated an IC<sub>50</sub> of 1.2  $\mu$ M in in vitro cytotoxicity  
 assay and a GI<sub>50</sub> of 1.0  $\mu$ M in tumor cell screening. Further aspects of the

present invention relate to their use in the manufacture of a medicament for the treatment of a proliferative disease.

IT 864767-64-6P

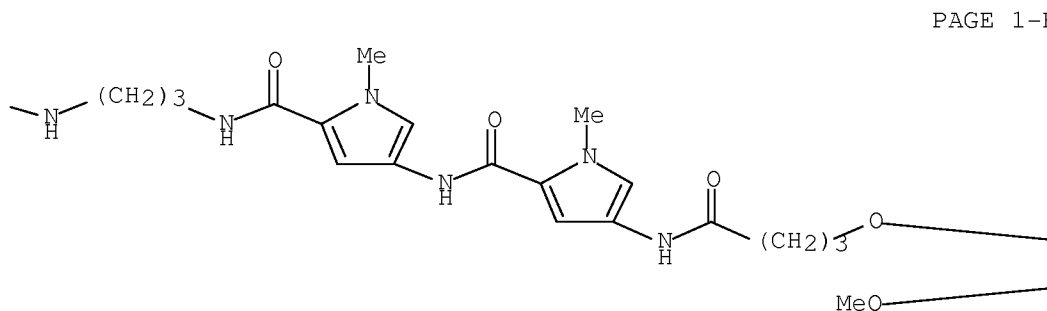
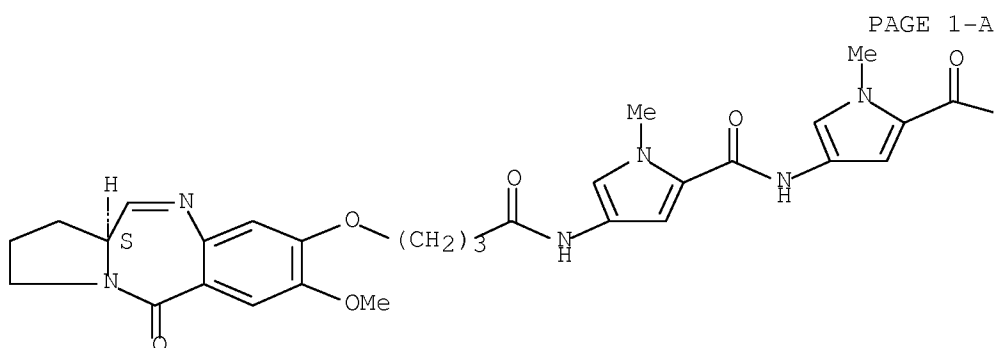
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

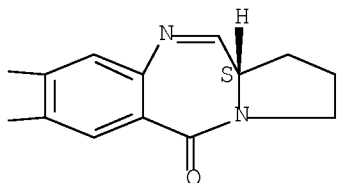
(drug candidate; preparation of oxotetrahydropyrrolobenzodiazepine dimers containing pyrroledicarboxylic acid amide linkers and oligomeric analogs thereof as antiproliferative agents)

RN 864767-64-6 CAPLUS

CN 1H-Pyrrole-2-carboxamide, N,N'-1,3-propanediylbis[1-methyl-4-[[[1-methyl-4-[[1-oxo-4-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]-1H-pyrrol-2-yl]carbonyl]amino]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).





IT 864767-37-3P 864767-40-8P 864767-42-0P  
 864767-53-3P 864767-63-5P 864767-65-7P  
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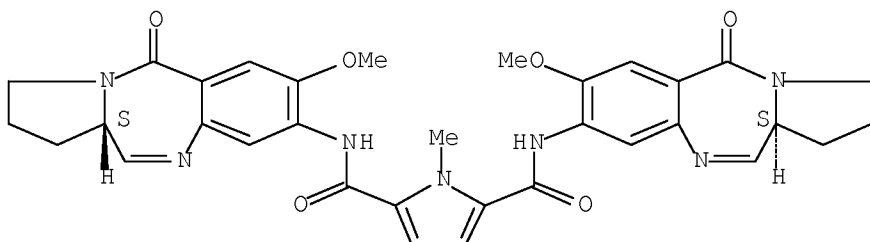
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
 (Uses)

(drug candidate; preparation of oxotetrahydropyrrolobenzodiazepine dimers  
 containing pyrroledicarboxylic acid amide linkers and oligomeric analogs  
 thereof as antiproliferative agents)

RN 864767-37-3 CAPLUS

CN 1H-Pyrrole-2,5-dicarboxamide, 1-methyl-N2,N5-bis[(11aS)-2,3,5,11a-  
 tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]- (CA  
 INDEX NAME)

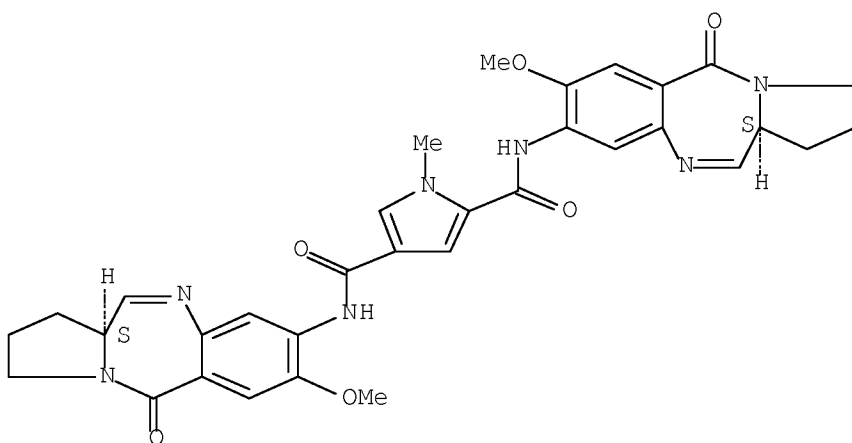
Absolute stereochemistry. Rotation (+).



RN 864767-40-8 CAPLUS

CN 1H-Pyrrole-2,4-dicarboxamide, 1-methyl-N2,N4-bis[(11aS)-2,3,5,11a-  
 tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]- (CA  
 INDEX NAME)

Absolute stereochemistry. Rotation (+).

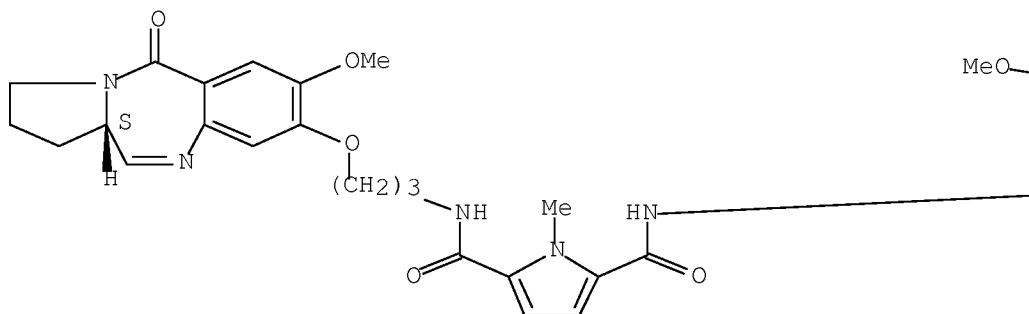


RN 864767-42-0 CAPLUS

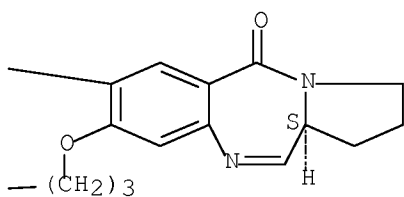
CN 1H-Pyrrole-2,5-dicarboxamide, 1-methyl-N2,N5-bis[3-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



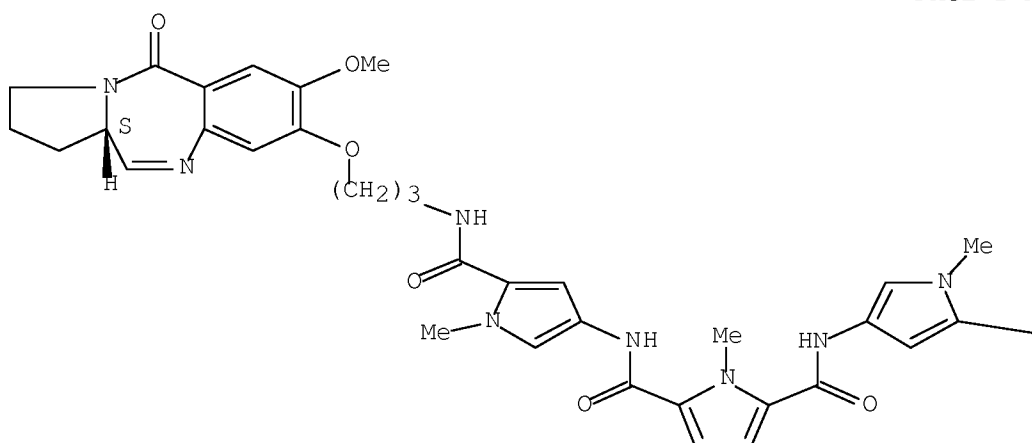
RN 864767-53-3 CAPLUS

CN 1H-Pyrrole-2,5-dicarboxamide, 1-methyl-N2,N5-bis[1-methyl-5-[[[3-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-

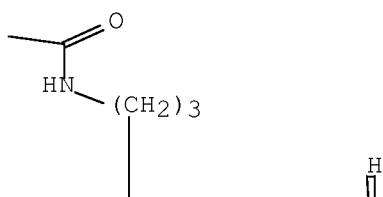
yl]oxy]propyl]amino]carbonyl]-1H-pyrrol-3-yl]- (CA INDEX NAME)

Absolute stereochemistry.

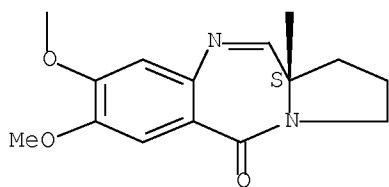
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PAGE 1-B



PAGE 2-B

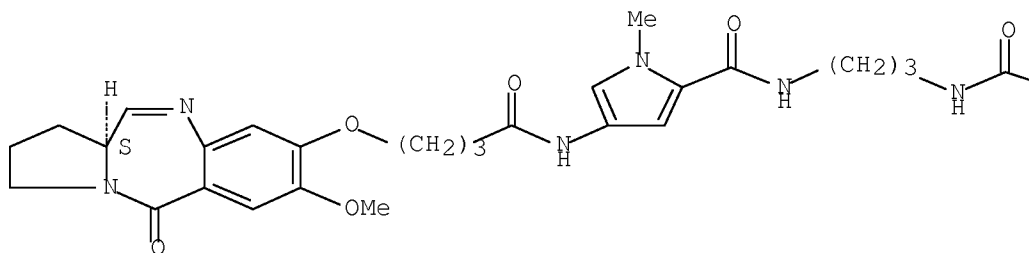


RN 864767-63-5 CAPLUS

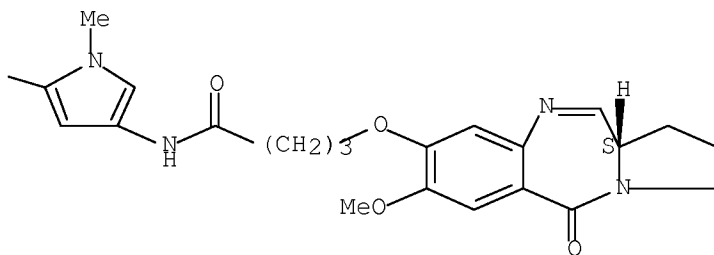
CN 1H-Pyrrole-2-carboxamide, N,N'-1,3-propanediylbis[1-methyl-4-[[1-oxo-4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]-

Absolute stereochemistry.

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PAGE 1-B



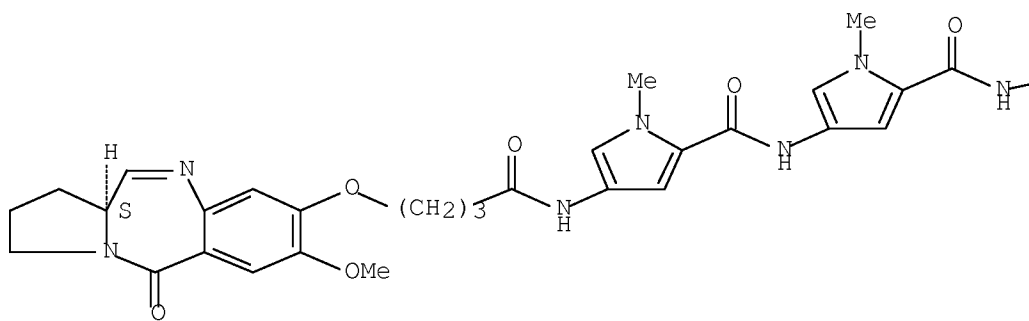
RN 864767-65-7 CAPLUS

CN 1H-Pyrrole-2-carboxamide, N,N'-1,3-propanediylbis[1-methyl-4-[[[1-methyl-4-[[[1-methyl-4-[[1-oxo-4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]-1H-pyrrol-2-yl]carbonyl]amino]-1H-pyrrol-2-yl]carbonyl]amino]-

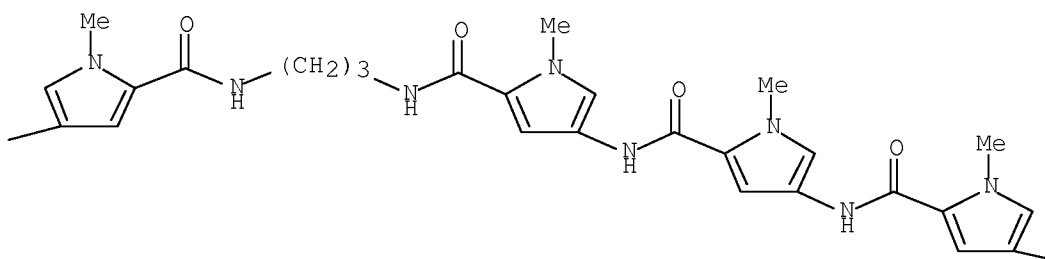
Absolute stereochemistry.



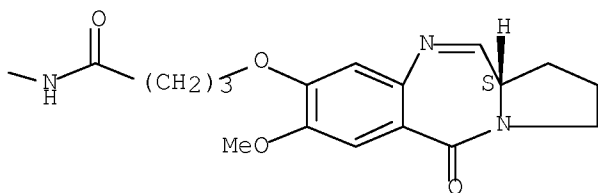
PAGE 1-A



PAGE 1-B



PAGE 1-C



RN 864767-66-8 CAPLUS  
 CN 1H-Pyrrole-2-carboxamide, 1-methyl-4-[[[1-methyl-4-[[1-oxo-4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]-1H-pyrrol-2-yl]carbonyl]amino]-N-[1-methyl-5-[[[3-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-

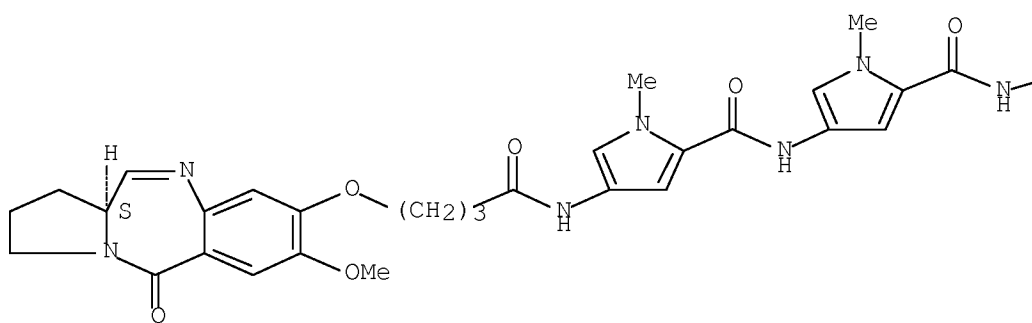
Absolute stereochemistry.

COC1=CC=C2C(=C1)C(=O)N3CCCC3S2=N
CCCC(=O)Nc1ccc(NC(=O)c2cc(NC(=O)O)cc2N)c1Cc1cc(C(=O)NCCOC2=CC=C(C(=O)N3C[C@H](CC3)S2)C=C2C)nc(C)c1

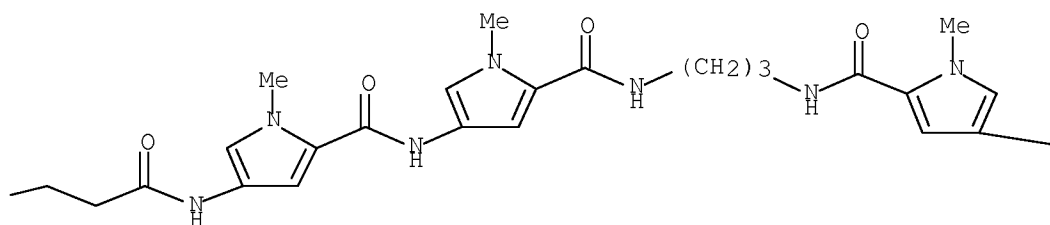
CN 1H-Pyrrole-2-carboxamide, N,N'-1,3-propanediylbis[1-methyl-4-[[[1-methyl-4-[[3-[[[1-methyl-4-[[[1-methyl-4-[1-oxo-4-[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]-1H-pyrrol-2-yl]carbonyl]amino]-1H-pyrrol-2-yl]carbonyl]amino]-1-oxopropyl]amino]-1H-pyrrol-2-yl]carbonyl]amino]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

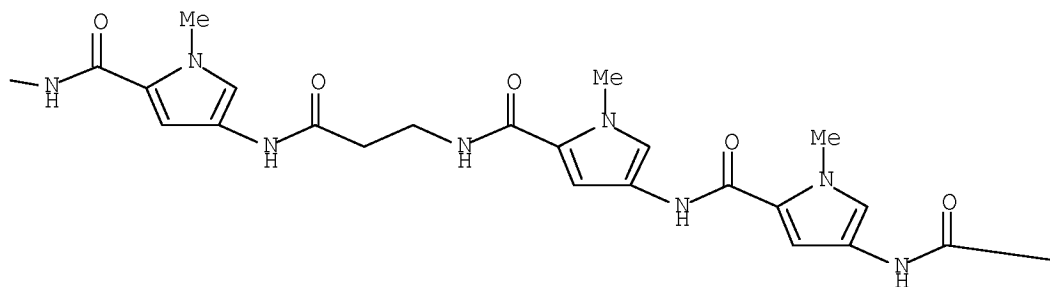
PAGE 1-A

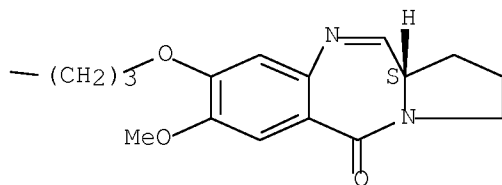


PAGE 1-B



PAGE 1-C

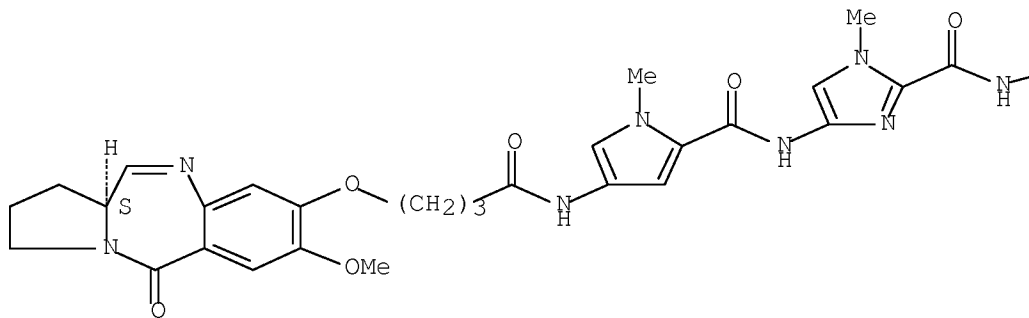




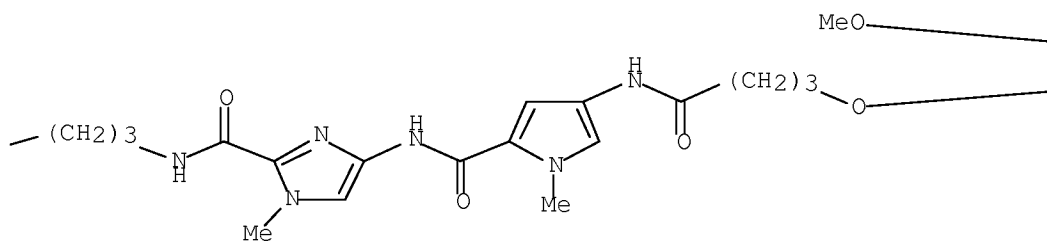
RN 864767-68-0 CAPLUS

CN 1H-Imidazole-2-carboxamide, N,N'-1,3-propanediylbis[1-methyl-4-[[[1-methyl-4-[[1-oxo-4-[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]-1H-pyrrol-2-yl]carbonyl]amino]-  
(CA INDEX NAME)

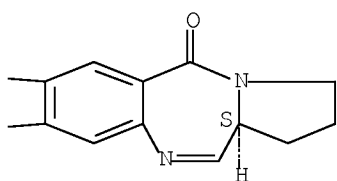
Absolute stereochemistry.



PAGE 1-B



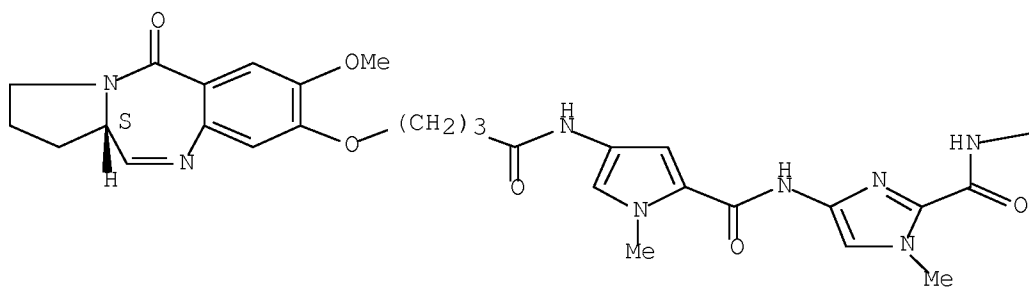
PAGE 1-C

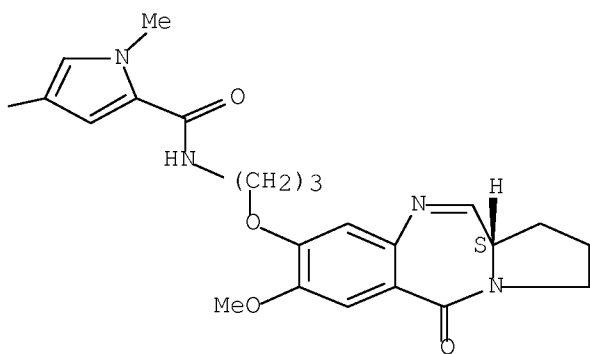


RN 864767-69-1 CAPLUS  
 CN 1H-Imidazole-2-carboxamide, 1-methyl-4-[[[1-methyl-4-[[1-oxo-4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]-1H-pyrrol-2-yl]carbonyl]amino]-N-[1-methyl-5-[[[3-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propyl]amino]carbonyl]-1H-pyrrol-3-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

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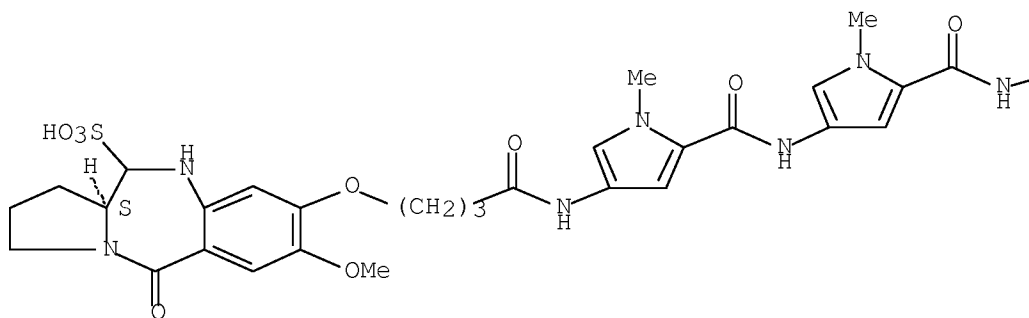




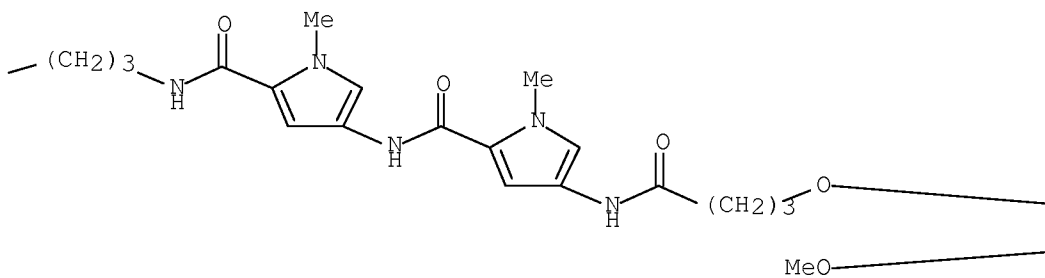
RN 864767-70-4 CAPLUS

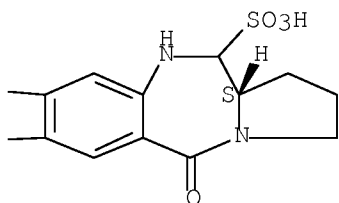
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-11-sulfonic acid,  
8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-pyrrole-2,4-  
diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)imino(4-oxo-4,1-  
butanediyl)oxy]]bis[2,3,5,10,11,11a-hexahydro-7-methoxy-5-oxo-, disodium  
salt, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 Na





IT 864672-61-7P 864672-62-8P 864672-68-4P  
 864672-70-8P 864672-73-1P 864672-75-3P  
 864672-77-5P 864672-83-3P 864672-90-2P  
 864672-92-4P 864672-96-8P

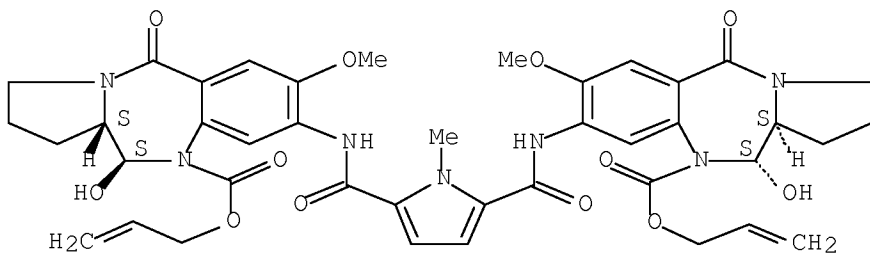
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of oxotetrahydropyrrolobenzodiazepine dimers containing pyrroledicarboxylic acid amide linkers and oligomeric analogs thereof as antiproliferative agents)

RN 864672-61-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[(1-methyl-1H-pyrrole-2,5-diyl)bis(carbonylimino)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

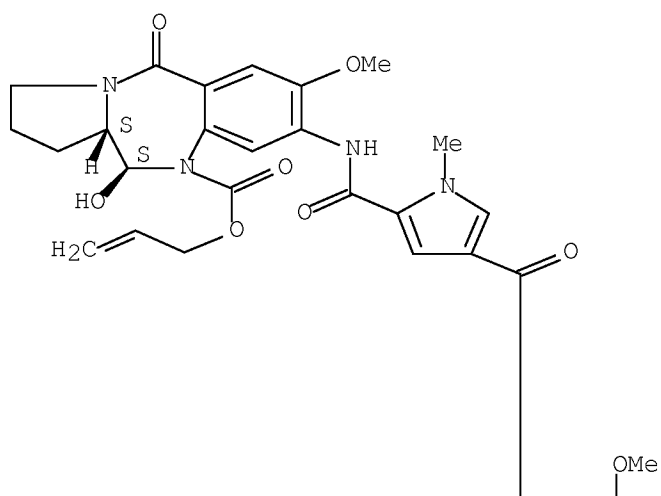


RN 864672-62-8 CAPLUS

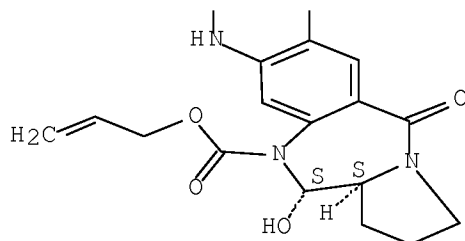
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[[[4-[[[(11S,11aS)-2,3,5,10,11,11a-hexahydro-11-hydroxy-7-methoxy-5-oxo-10-[(2-propen-1-yloxy)carbonyl]-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]amino]carbonyl]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

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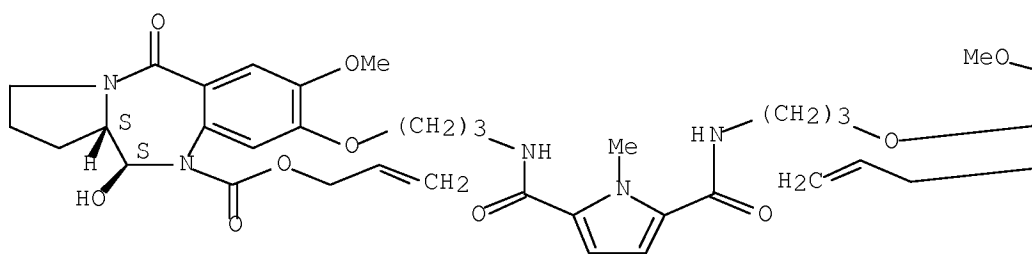
PAGE 2-A



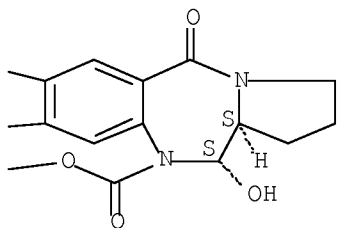
RN 864672-68-4 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[(1-methyl-1H-pyrrole-2,5-diyl)bis(carbonylimino-3,1-  
 propanediylloxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-,  
 di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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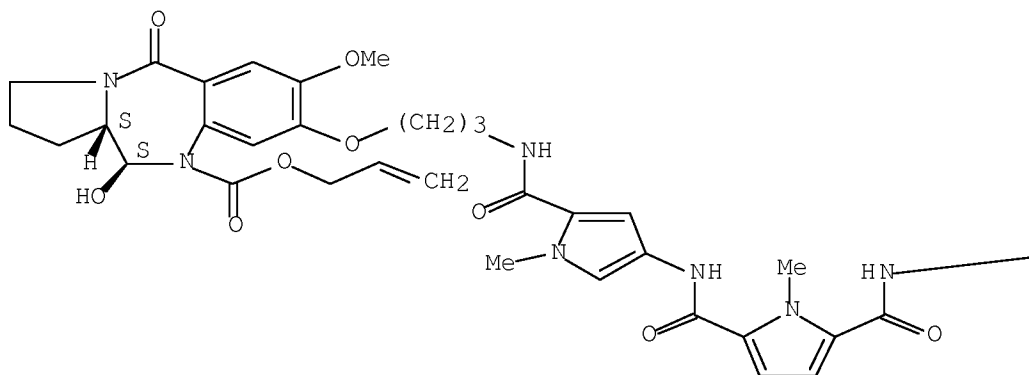


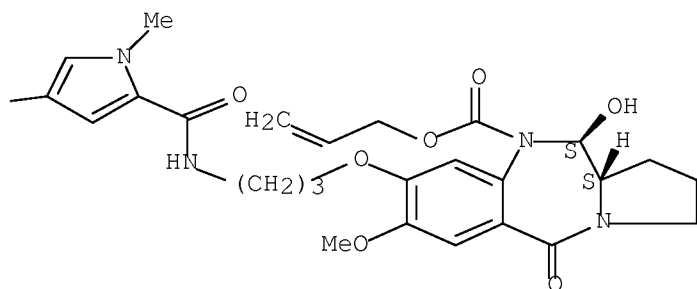




RN 864672-70-8 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[(1-methyl-1H-pyrrole-2,5-diyl)bis(carbonylimino(1-methyl-1H-pyrrole-  
 4,2-diyl)carbonylimino-3,1-propanediolyloxy)]bis[2,3,11,11a-tetrahydro-11-  
 hydroxy-7-methoxy-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-  
 (9CI) (CA INDEX NAME)

Absolute stereochemistry.

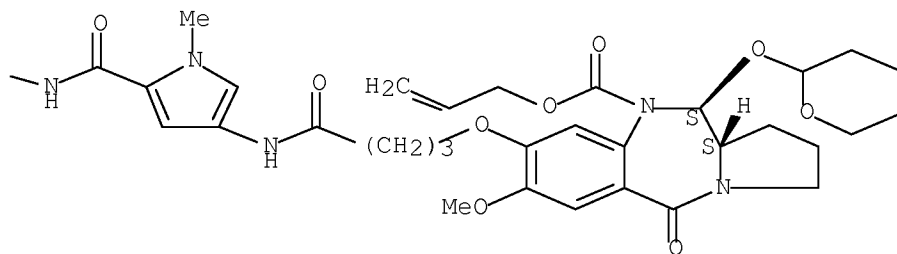
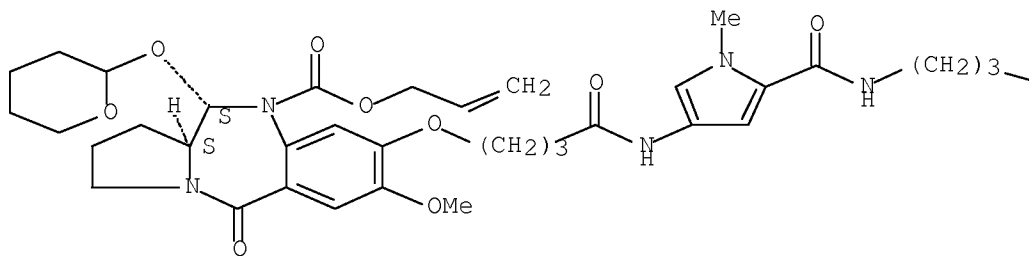




RN 864672-73-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-pyrrole-2,4-  
diyl)imino(4-oxo-4,1-butanediyl)oxy]]bis[2,3,11,11a-tetrahydro-7-methoxy-5-  
oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, di-2-propenyl ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

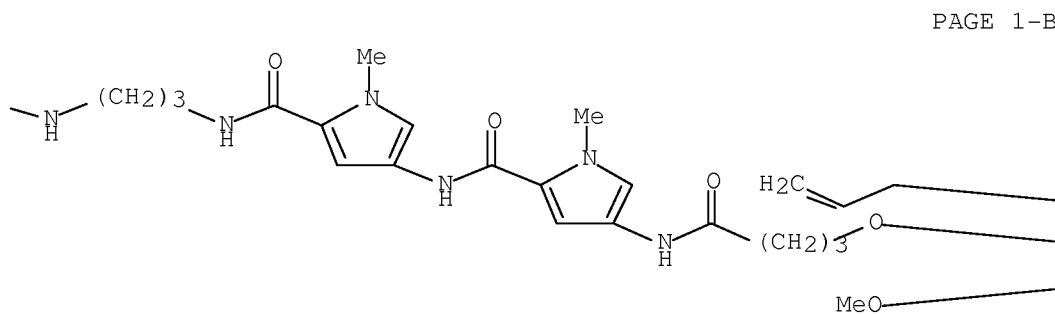
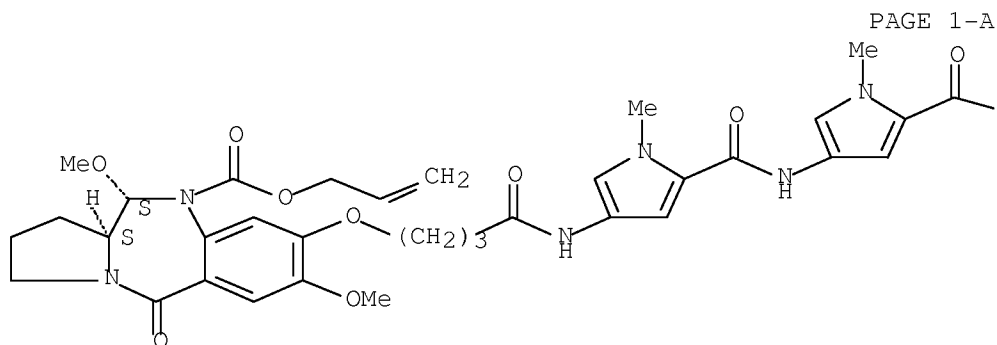
Absolute stereochemistry.



RN 864672-75-3 CAPLUS

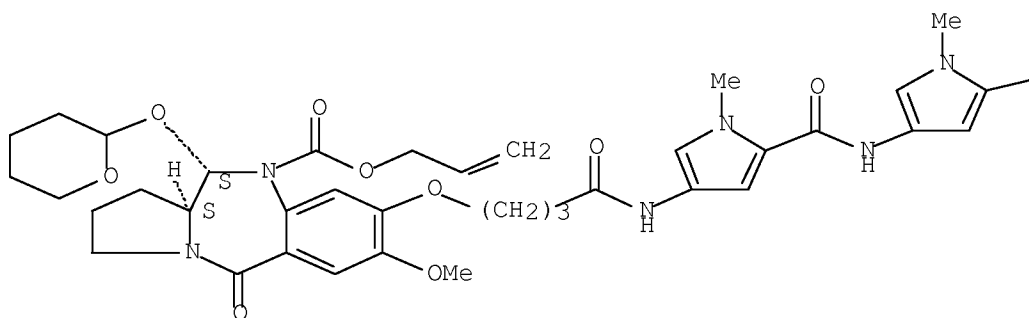
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-pyrrole-2,4-  
diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)imino(4-oxo-4,1-  
butanediyl)oxy]]bis[2,3,11,11a-tetrahydro-7,11-dimethoxy-5-oxo-,  
di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

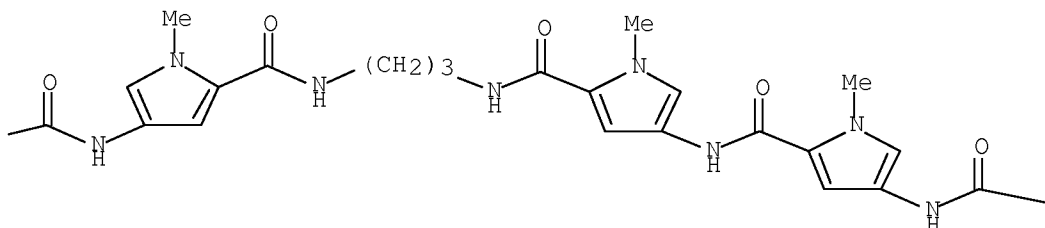


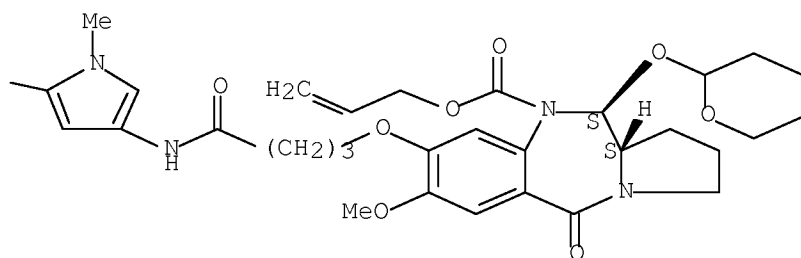
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-pyrrole-2,4-  
diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)iminocarbonyl(1-methyl-1H-  
pyrrole-2,4-diyl)imino(4-oxo-4,1-butanediyl)oxy]]bis[2,3,11,11a-tetrahydro-  
7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, di-2-propenyl ester,  
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

PAGE 1-A



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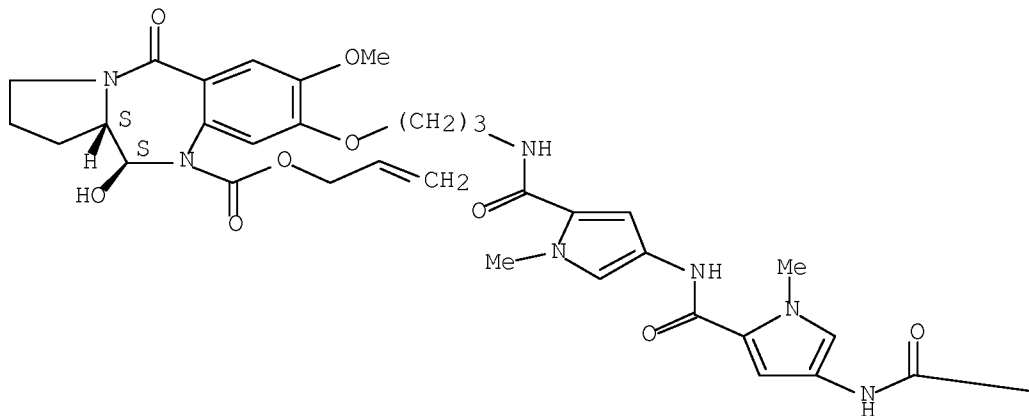


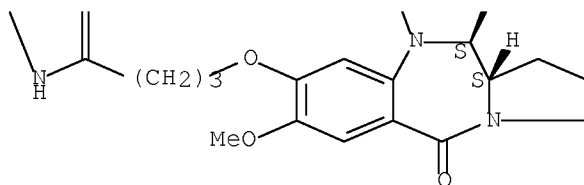
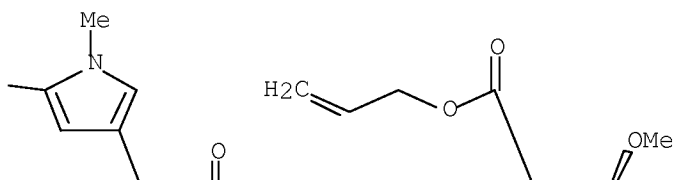


RN 864672-83-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8-[3-[[[4-[[[4-[[[4-[[4-[(11S,11aS)-2,3,5,10,11,11a-hexahydro-7,11-  
dimethoxy-5-oxo-10-[(2-propen-1-yloxy)carbonyl]-1H-pyrrolo[2,1-  
c][1,4]benzodiazepin-8-yl]oxy]-1-oxobutyl]amino]-1-methyl-1H-pyrrol-2-  
yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-  
pyrrol-2-yl]carbonyl]amino]propoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-  
methoxy-5-oxo-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

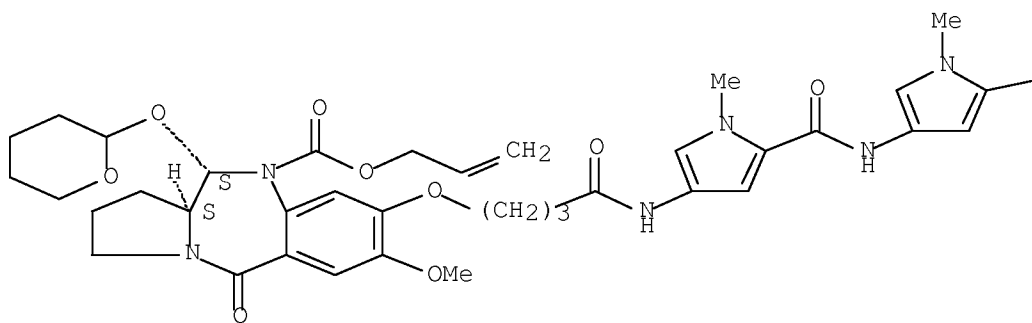




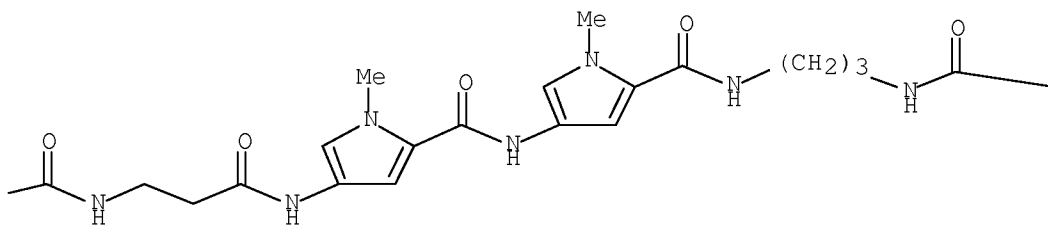
RN 864672-90-2 CAPLUS  
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 diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)imino(3-oxo-3,1-  
 propanediyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)iminocarbonyl(1-  
 methyl-1H-pyrrole-2,4-diyl)imino(4-oxo-4,1-butanediyl)oxy]]bis[2,3,11,11a-  
 tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-,  
 di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

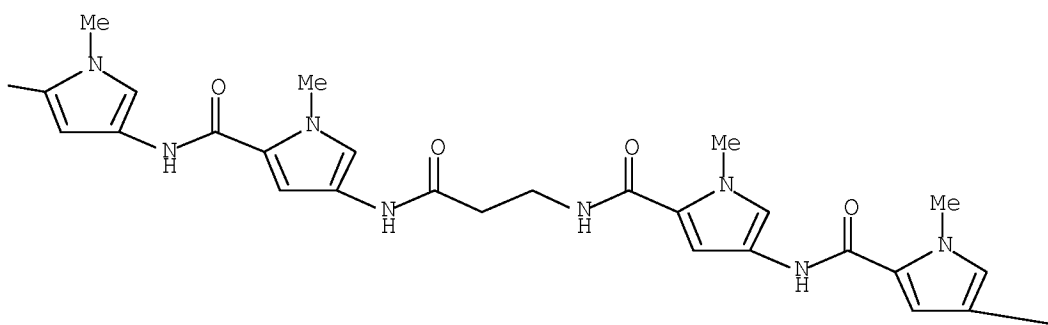
PAGE 1-A

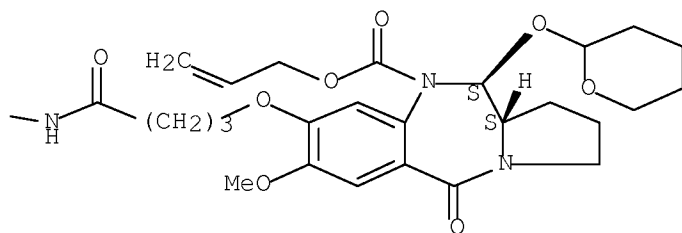


PAGE 1-B



PAGE 1-C

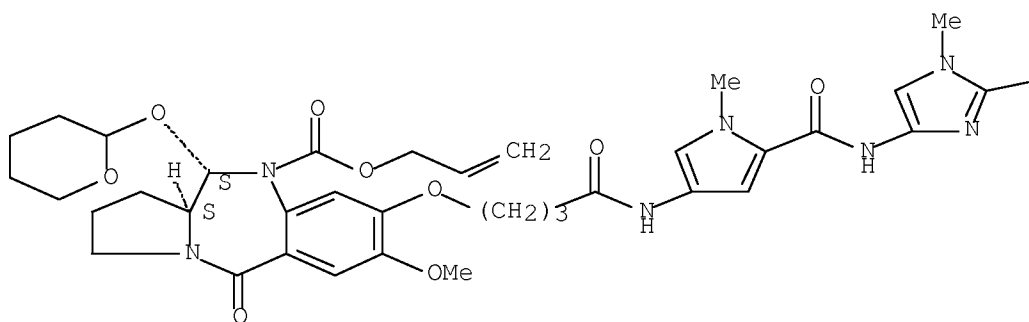




RN 864672-92-4 CAPLUS

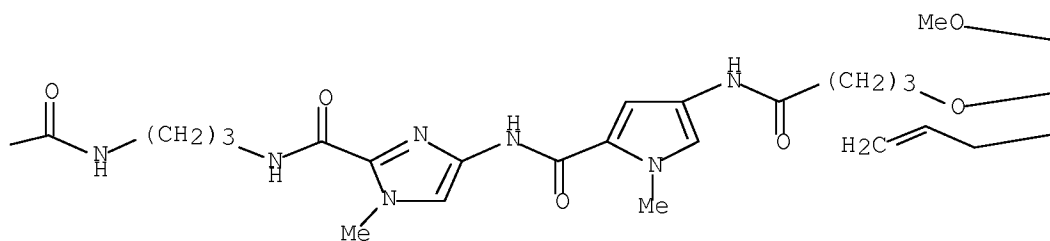
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-imidazole-2,4-  
diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)imino(4-oxo-4,1-  
butanediyl)oxy]]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-  
2H-pyran-2-yl)oxy]-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

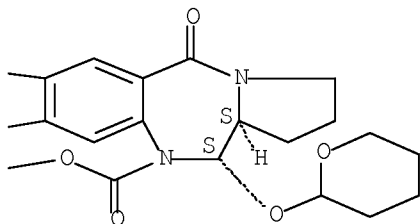




PAGE 1-B



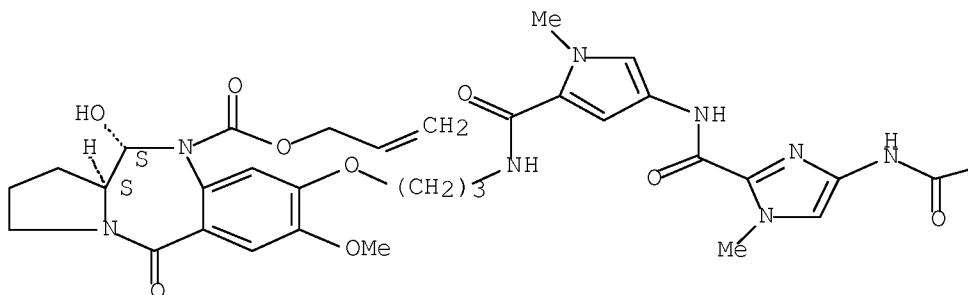
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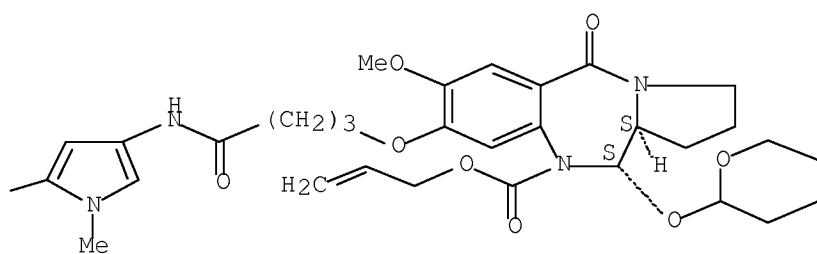


RN 864672-96-8 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8-[4-[[5-[[[2-[[[5-[[[3-[[[11S,11aS)-2,3,5,10,11,11a-hexahydro-11-hydroxy-  
 7-methoxy-5-oxo-10-[(2-propen-1-yloxy)carbonyl]-1H-pyrrolo[2,1-  
 c][1,4]benzodiazepin-8-yl]oxy]propyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-  
 yl]amino]carbonyl]-1-methyl-1H-imidazol-4-yl]amino]carbonyl]-1-methyl-1H-  
 pyrrol-3-yl]amino]-4-oxobutoxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-  
 [(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propen-1-yl ester, (11S,11aS)- (CA  
 INDEX NAME)

Absolute stereochemistry.

PAGE 1-A





RE.CNT 3      THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 31 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:996025 CAPLUS Full-text

DN 143:338869

TI Validation and Development of a Predictive Paradigm for Hemotoxicology  
Using a Multifunctional Bioluminescence Colony-Forming Proliferation Assay

AU Rich, Ivan N.; Hall, Karen M.

CS HemoGenix, Inc, Colorado Springs, CO, 80907, USA

SO Toxicological Sciences (2005), 87(2), 427-441

CODEN: TOSCF2; ISSN: 1096-6080

PB Oxford University Press

DT Journal

LA English

AB The lympho-hematopoietic colony-forming assay has been redesigned into a rapid, nonsubjective and standardized proliferation assay that can measure the effects of compds. on multiple stem and progenitor cell populations from different species simultaneously using a sensitive, high-throughput bioluminescence readout. Eleven reference compds. from the Registry of Cytotoxicity (RC) and eight other compds., including anticancer drugs, were studied over an 8- to 9-log dose range for their effects on seven cell populations from both human and mouse bone marrow simultaneously. The cell populations studied included a primitive (HPP-SP) and mature (CFC-GEMM) stem cell, three hematopoietic (BFU-E, GM-CFC, Mk-CFC) and two lymphopoietic (T-CFC, B-CFC) populations. The results reveal a five-point prediction paradigm for lympho-hematotoxicity. Depending on how and which populations are affected, the resulting effects in the periphery can be predicted. Validation against the RC Prediction Model produces a high degree of correlation between the in vitro IC50 values and known in vivo LD50 values, thereby allowing preclin. dosing to be predicted. If primary human hematopoietic target tissue is used, inhibitory concentration (IC50/IC75/IC90) values of anticancer and other drugs can be converted into predicted clin. doses which, when compared to published chemotherapeutic dosing regimen, are very similar. When performed during early drug screening, the prediction value of the assay should help reduce time and cost, but above all, provide increase efficacy and safety for the patient.

IT 232931-57-6, Sjg-136

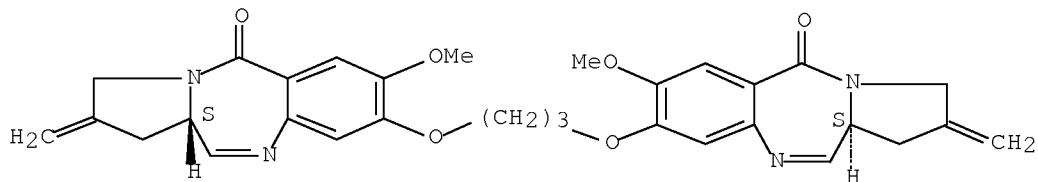
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(validation and development of predictive paradigm for hemotoxicol.  
using multifunctional bioluminescence colony-forming proliferation  
assay)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-,  
(11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



L18 ANSWER 32 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:995985 CAPLUS Full-text

DN 144:270370

TI Pyrrolobenzodiazepine dimers: Novel sequence-selective, DNA-interactive, cross-linking agents with activity against Gram-positive bacteria

AU Hadjivassileva, Tsveta; Thurston, David E.; Taylor, Peter W.

CS School of Pharmacy, London, WC1N 1AX, UK

SO Journal of Antimicrobial Chemotherapy (2005), 56(3), 513-518

CODEN: JACHDX; ISSN: 0305-7453

PB Oxford University Press

DT Journal

LA English

AB Objectives: Pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimers are synthetic sequence-selective interstrand DNA minor-groove crosslinking agents developed from anthramycins. We investigated the antibacterial activity of three dimers, SJG-136, DRG-16 and ELB-21, which differ in the structure of the PBD monomeric unit and the length of the linker region between the two identical PBD monomers. Methods: MICs were determined against 38 methicillin-resistant *Staphylococcus aureus* (MRSA), 20 vancomycin-resistant enterococci (VRE), 12 isolates of *Streptococcus pyogenes*, 12 of *Streptococcus agalactiae*, 12 of *Listeria monocytogenes* and 24 Gram-neg. clin. isolates. Binding to double-stranded DNA was assessed by determination of the DNA melting temperature ( $T_m$ ). Results: MIC90 values for SJG-136 were 0.5 mg/L against MRSA, VRE and *L. monocytogenes*, 0.06 mg/L against *S. pyogenes* and 0.03 mg/L against *S. agalactiae*; these were below the maximum tolerated dose of the drug. MIC90s for DRG-16 were 0.125, >0.5, 0.125, 0.015 and <0.008 mg/L, resp. The most potent compound was ELB-21, with corresponding MIC90 values of 0.03, 0.06, 0.06, 0.015 and 0.015 mg/L. There was little or no variation in sensitivity amongst isolates from any one species. All Gram-neg. species (*Acinetobacter*, *Pseudomonas*, *Klebsiella*, *Proteus* spp.) were not susceptible due to the barrier function of the outer membrane. PBD dimers showed bactericidal activity against MRSA and VRE and there was a significant post-antibiotic effect (1.5-3.5 h). Incubation of EMRSA-16 genomic DNA (50  $\mu$ M) with 20  $\mu$ M ELB-21 resulted in a large increase in  $T_m$  suggesting that PBD dimers exert their antibacterial effect by crosslinking of the two DNA strands. Conclusions: These data indicate that this novel class of antibacterial agents warrants further investigation as potential antibiotics for the treatment of severe infections caused by Gram-pos. pathogens.

IT 232931-57-6, SJG 136 260417-62-7, DRG 16

877659-86-4, ELB 21

RL: BSU (Biological study, unclassified); BIOL (Biological study)

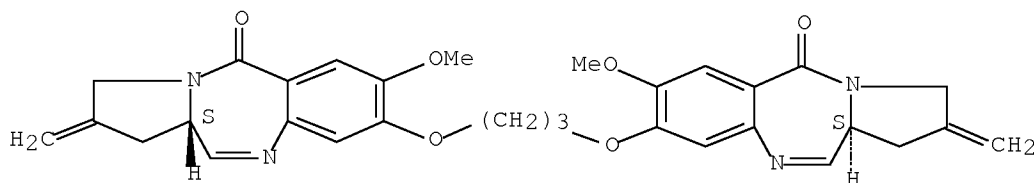
(pyrrolobenzodiazepine dimers as novel sequence-selective,

DNA-interactive, crosslinking agents with activity against Gram-pos. bacteria)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

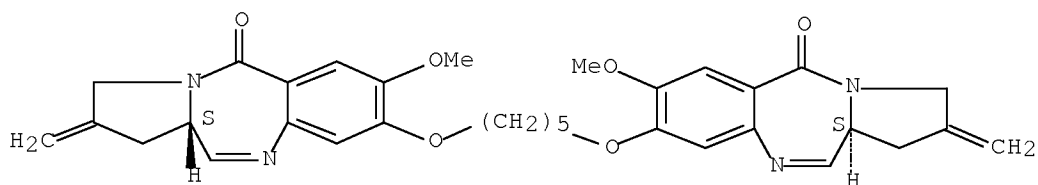
Absolute stereochemistry. Rotation (+).



RN 260417-62-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediy]bis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

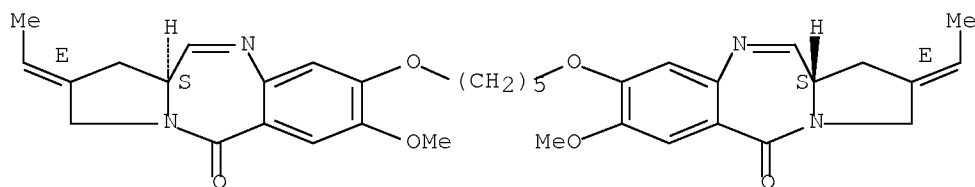


RN 877659-86-4 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediy]bis(oxy)]bis[2-ethylidene-1,2,3,11a-tetrahydro-7-methoxy-, (2E,2'E,11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.



RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 33 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:761162 CAPLUS Full-text

DN 144:257

TI Influence of P-glycoprotein expression on in vitro cytotoxicity and in vivo antitumour activity of the novel pyrrolobenzodiazepine dimer SJG-136

AU Guichard, S. M.; Macpherson, J. S.; Thurston, D. E.; Jodrell, D. I.

CS Pharmacology and Drug Development Team, Cancer Research UK Centre, Western General Hospital, University of Edinburgh, Edinburgh, EH4 2XR, UK

SO European Journal of Cancer (2005), 41(12), 1811-1818

CODEN: EJCAEL; ISSN: 0959-8049

PB Elsevier Ltd.

DT Journal

LA English

AB SJG-136 is a novel pyrrolobenzodiazepine dimer analog that acts as a minor-groove interstrand DNA crosslinking agent. The present study investigated the impact of ABCB1 (mdr-1) expression on the activity of SJG-136 using both in vitro and in vivo systems. SJG-136 was highly potent in the colon cancer cell lines HCT-116, HT-29 and SW620 (IC<sub>50</sub> 0.1-0.3 nM). However, HCT-8 and HCT-15 cells expressing significant levels of mdr-1 were less sensitive (IC<sub>50</sub> 2.3 and 3.7 nM, resp.) using a SRB assay. The cytotoxicity was increased in HCT-15 and A2780AD in presence of 5 µg/mL verapamil. Mdr-1 mRNA expression was determined by qRT-PCR and correlated to SJG-136 IC<sub>50</sub>s (r<sup>2</sup> = 0.86, P = 0.0001). Isogenic 3T3 cells expressing mdr-1 cDNA (3T3 pHamdr-1) were less sensitive to SJG-136 than the parental 3T3 cells (IC<sub>50</sub> 208 and 6.3 nM, resp.). Finally, SJG-136 (120 µg/kg/d dx5) was highly active against A2780 xenografts (SGD = 275) but not A2780AD xenografts (SGD = 67).

IT 232931-57-6, SJG-136

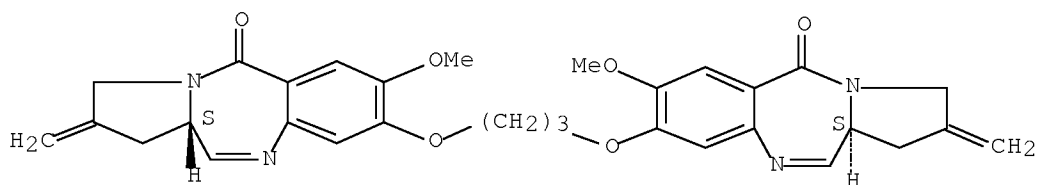
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pyrrolobenzodiazepine dimer, SJG-136 was cytotoxic in colon cancer cell lines but HCT-8 and HCT-15 cell lines expressing mdr-1 were less sensitive and showed antitumor activity against A2780 but not A2780AD xenografts in mouse)

RN 232931-57-6 CAPLUS

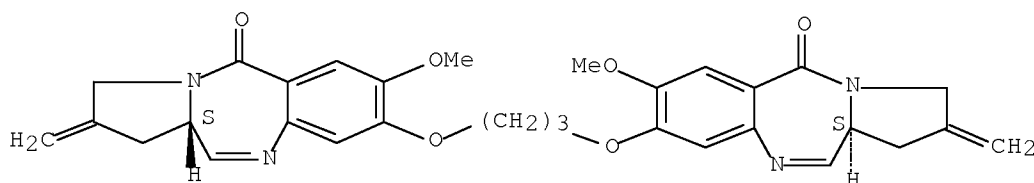
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L18 ANSWER 34 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:647488 CAPLUS Full-text  
 DN 143:292707  
 TI Direct liquid chromatography determination of the reactive imine SJG-136 (NSC 694501)  
 AU Cheung, Andrew; Struble, Elaine; He, Jingyi; Yang, Chun; Wang, Euphemia; Thurston, David E.; Liu, Paul  
 CS Analytical Chemistry Department, SRI International, Menlo Park, CA, 94025, USA  
 SO Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2005), 822(1-2), 10-20  
 CODEN: JCBAAI; ISSN: 1570-0232  
 PB Elsevier B.V.  
 DT Journal  
 LA English  
 AB SJG-136 (NSC 694501), 8,8'-[[[(propane-1,3-diyl)dioxy]bis[(11aS)-7-methoxy-2-methylidene-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4] benzodiazepin-5-one]], which is being developed as a DNA-interactive antitumor agent, contains highly reactive imines in the diazepinone portions of the mol. Water or alc. adds readily to the imino moiety to form the corresponding carbinolamine or its alkyl ether, resp. This sensitivity to protic substances poses a formidable challenge to the formulation and HPLC assay development for the compound. After studying the solution chemical of SJG-136 and its potential interaction with various stationary phases, two reversed-phase liquid chromatog. assays for the compound have been developed. A direct assay that separates SJG-136 from its water or methanol adducts and an indirect assay that quantifies SJG-136 as its dihydrate adduct are reported. The latter method, which is more practical for drug development, has been validated. It is reproducible (R.S.D. < 2%), linear ( $r^2 = 0.9999$ ) and accurate (within 98-102% recovery), with a lower detection limit of 2.5 ng.  
 IT 232931-57-6, SJG-136  
 RL: ANT (Analyte); ANST (Analytical study)  
 (direct liquid chromatog. determination of the reactive imine SJG-136)  
 RN 232931-57-6 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

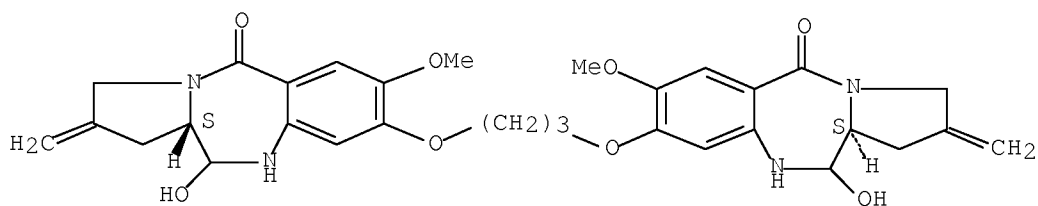
Absolute stereochemistry. Rotation (+).



IT 851177-99-6 851178-00-2  
 RL: FMU (Formation, unclassified); PRP (Properties); FORM (Formation, nonpreparative)  
 (direct liquid chromatog. determination of the reactive imine SJG-136)  
 RN 851177-99-6 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-11-hydroxy-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)



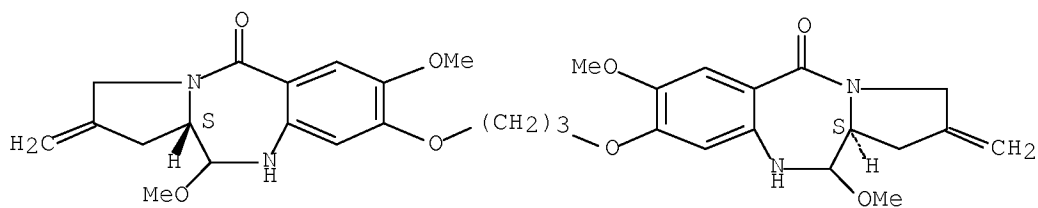
Absolute stereochemistry.



RN 851178-00-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7,11-dimethoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 35 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:646535 CAPLUS Full-text

DN 143:166214

TI The XPF-ERCC1 endonuclease and homologous recombination contribute to the repair of minor groove DNA interstrand crosslinks in mammalian cells produced by the pyrrolo[2,1-c][1,4]benzodiazepine dimer SJG-136

AU Clingen, Peter H.; De Silva, Inusha U.; McHugh, Peter J.; Ghadessy, Farid J.; Tilby, Michael J.; Thurston, David E.; Hartley, John A.

CS Cancer Research UK Drug-DNA Interactions Research Group, Department of Oncology, Royal Free and University College Medical School, UCL, London, W1W 7BS, UK

SO Nucleic Acids Research (2005), 33(10), 3283-3291

CODEN: NARHAD; ISSN: 0305-1048

PB Oxford University Press

DT Journal

LA English

AB SJG-136, a pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimer, is a highly efficient interstrand crosslinking agent that reacts with guanine bases in a 5'-GATC-3' sequence in the DNA minor groove. SJG-136 crosslinks form rapidly and persist compared to those produced by conventional crosslinking agents such as nitrogen mustard, melphalan or cisplatin which bind in the DNA major groove. A panel of Chinese hamster ovary (CHO) cells with defined defects in specific DNA repair pathways were exposed to the bi-functional agents SJG-136 and melphalan, and to their mono-functional analogs mmy-SJG and mono-functional melphalan. SJG-136 was >100 times more cytotoxic than melphalan, and the bi-functional agents were much more cytotoxic than their resp. mono-functional analogs. Cellular sensitivity of both SJG-136 and melphalan was dependent on the XPF-ERCC1 heterodimer, and homologous recombination repair factors XRCC2 and XRCC3. The relative level of sensitivity of these repair mutant cell lines to SJG-136 was, however, significantly less than with major groove crosslinking agents. In contrast to melphalan, there was no clear correlation between sensitivity to SJG-136 and crosslink unhooking capacity measured using a modified comet assay. Furthermore, repair of SJG-136 crosslinks did not involve the formation of DNA double-strand breaks. SJG-136 cytotoxicity is likely to result from the poor recognition of DNA damage by repair proteins resulting in the slow repair of both mono-adducts and more importantly crosslinks in the minor groove.

IT 232931-57-6, SJG-136

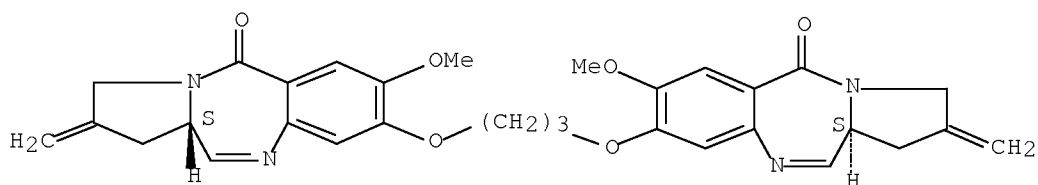
RL: PAC (Pharmacological activity); BIOL (Biological study)

(XPF-ERCC1 endonuclease and homologous recombination contribute to the repair of minor groove DNA interstrand crosslinks in mammalian cells produced by the pyrrolo[2,1-c][1,4]benzodiazepine dimer SJG-136)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

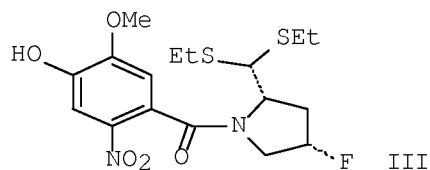
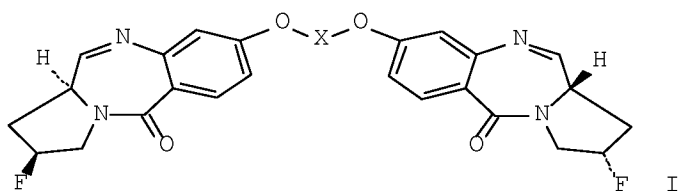
Absolute stereochemistry. Rotation (+).



RE.CNT 37      THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 36 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:612296 CAPLUS Full-text  
 DN 143:133404  
 TI A preparation of fluoropyrrolobenzodiazepine dimers, useful as antitumor agents  
 IN Kamal, Ahmed; Reddy, Peram Surakattula Murali Mohan; Reddy, Depatla Rajasekhara  
 PA Council of Scientific and Industrial Research, India  
 SO PCT Int. Appl., 28 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005063758	A1	20050714	WO 2003-IN448	20031231
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003300705	A1	20050721	AU 2003-300705	20031231
	GB 2425309	A	20061025	GB 2006-14749	20031231
	JP 2007518671	T	20070712	JP 2005-512747	20031231
	IN 2005DN01270	A	20071207	IN 2005-DN1270	20050331
PRAI	WO 2003-IN448	A	20031231		
OS	CASREACT 143:133404				
GI					



AB The invention relates to a preparation of fluoropyrrolobenzodiazepine dimers of formula I [wherein: X is (CH<sub>2</sub>)<sub>3-10</sub>], useful as antitumor agents. For instance, fluoropyrrolobenzodiazepine dimer II (I, X = CH<sub>2</sub>)<sub>4</sub>; (logGI<sub>50</sub> = -5.21, logTGI<sub>50</sub> = -4.75) was prepared from diethylthioacetal derivative III via 3 steps.

IT 717920-82-6P 717920-83-7P 717920-84-8P  
858639-17-5P 858639-19-7P 858639-21-1P  
858639-23-3P 858639-25-5P

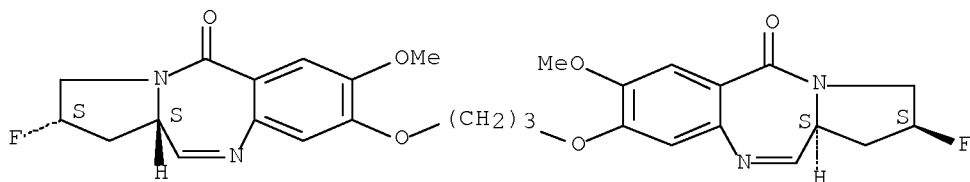
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
(Uses)

(preparation of fluoropyrrolobenzodiazepine dimers useful as antitumor  
agents)

RN 717920-82-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
propanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-,  
(2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

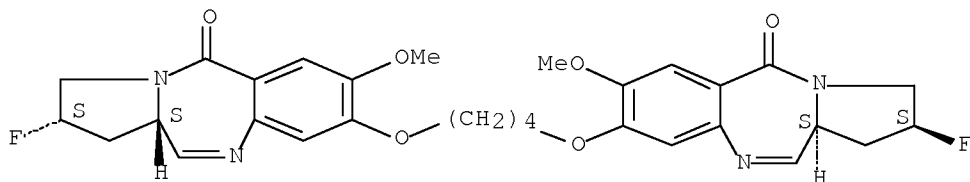
Absolute stereochemistry.



RN 717920-83-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-  
butanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-,  
(2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

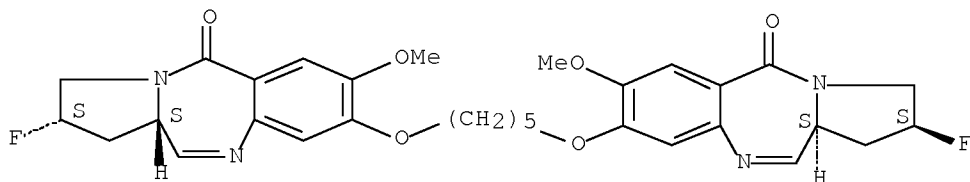
Absolute stereochemistry.



RN 717920-84-8 CAPLUS

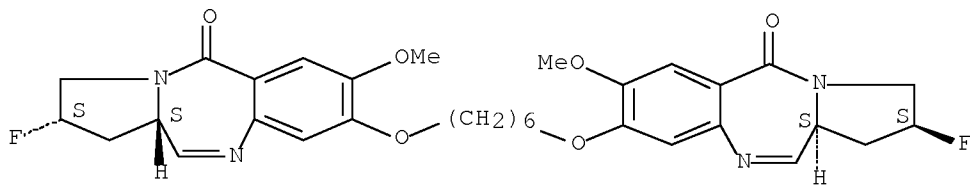
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-  
pentanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-,  
(2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



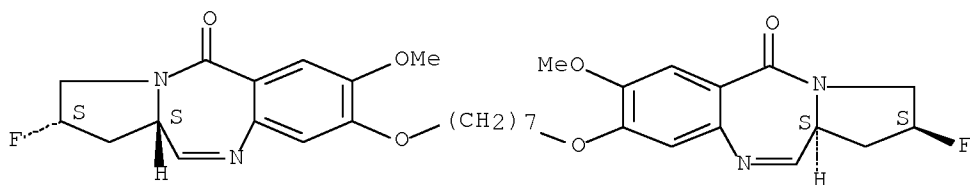
RN 858639-17-5 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,6-hexanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



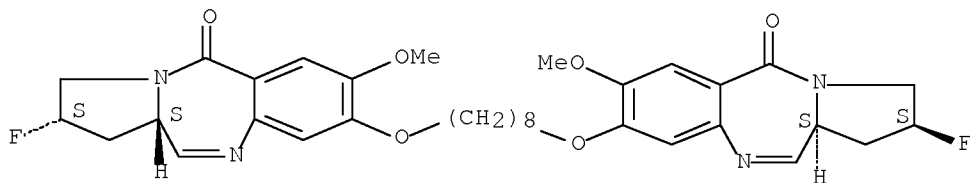
RN 858639-19-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,7-heptanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



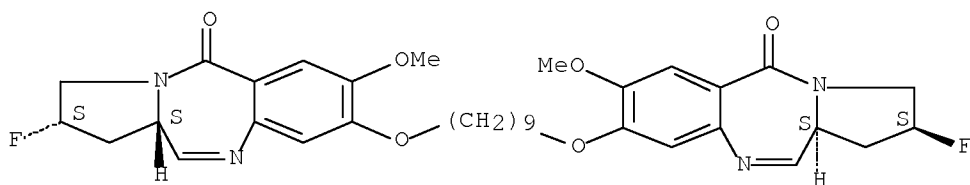
RN 858639-21-1 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,8-octanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 858639-23-3 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,9-nonanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

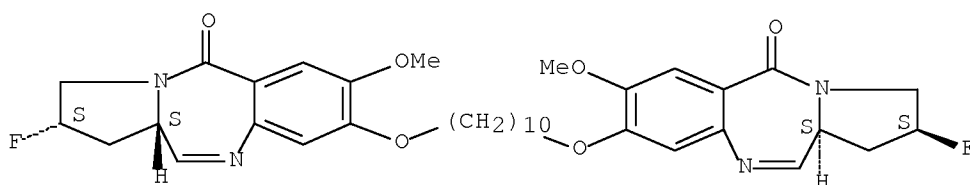
Absolute stereochemistry.



RN 858639-25-5 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,10-decanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-, (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 37 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
AN 2005:511193 CAPLUS Full-text  
DN 143:193982  
TI Design, synthesis and in vitro cytotoxic studies of novel  
bis-pyrrolo[2,1][1,4] benzodiazepine-pyrrole and imidazole polyamide  
conjugates  
AU Kumar, Rohtash; Lown, J. William  
CS Department of Chemistry, University of Alberta, Edmonton, AB, T6G 2G2,  
Can.  
SO European Journal of Medicinal Chemistry (2005), 40(7), 641-654  
CODEN: EJMCA5; ISSN: 0223-5234  
PB Elsevier Ltd.  
DT Journal  
LA English  
OS CASREACT 143:193982  
GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The design, synthesis and biol. evaluation of pyrrolo[2,1][1,4]benzodiazepine  
(PBD) dimers, e.g., I, linked with pyrrole and imidazole polyamides from  
either side by a flexible methylene chain of variable length are described,  
which involved mercuric chloride mediated cyclization of the corresponding  
amino di-Et thioacetals. The compds. were prepared with varying nos. of  
pyrrole and imidazole containing polyamides to determine the structural  
requirements for optimal in vitro antitumor activity. These compds. were  
tested against a panel of 60 human cancer cells by the National Cancer  
Institute, and demonstrated that, of the compds. bis-PBD-pyrrole polyamides  
(38-40) and bis-PBD-imidazole polyamides (41-43) certain of the bis-PBD-  
pyrrole and imidazole polyamide conjugates are active for individual cancer  
cell lines (Table 1). However, this study found that bis-PBD-pyrrole and  
imidazole polyamide conjugates in general were potent against many human  
cancer cell lines.

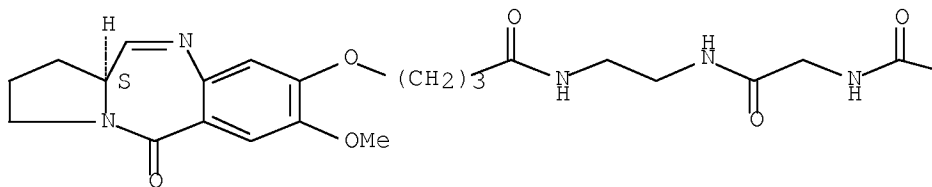
IT 861960-16-9P 861960-17-0P 861960-18-1P  
861960-19-2P 861960-20-5P 861960-21-6P  
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic  
preparation); BIOL (Biological study); PREP (Preparation)  
(preparation, anticancer, and structure-activity relationship of  
bis(pyrrolodibenzodiazepine)pyrroles and -imidazoles starting from  
[(carboxypropoxy)methoxy(nitro)benzoyl]pyrrolidinecarboxaldehyde  
dithioacetal)

RN 861960-16-9 CAPLUS  
CN 1H-Pyrrole-2-carboxamide, 1-methyl-N-[2-oxo-2-[[2-[[1-oxo-4-[[[(11aS)-  
2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-  
yl]oxy]butyl]amino]ethyl]amino]ethyl]-4-[[1-oxo-4-[[[(11aS)-2,3,5,11a-  
tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-  
yl]oxy]butyl]amino]- (CA INDEX NAME)

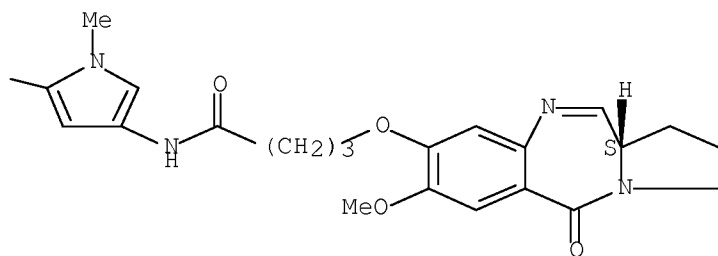
Absolute stereochemistry.



PAGE 1-A



PAGE 1-B

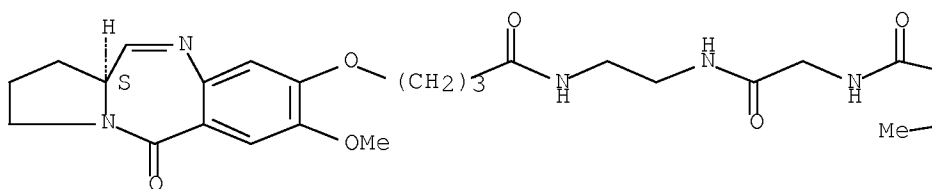


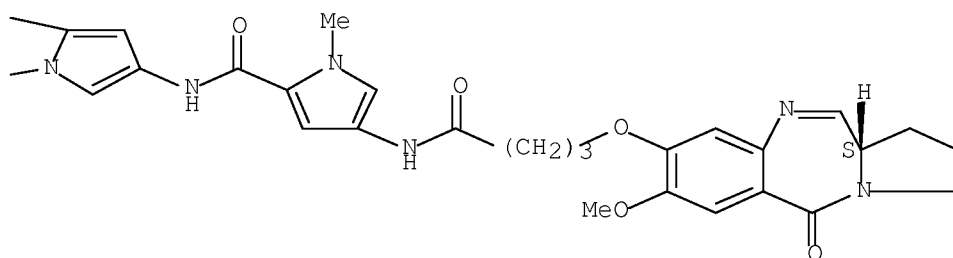
RN 861960-17-0 CAPLUS

CN 1H-Pyrrole-2-carboxamide, 1-methyl-N-[1-methyl-5-[[[2-oxo-2-[[2-[[1-oxo-4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]ethyl]amino]ethyl]amino]carbonyl]-1H-pyrrol-3-yl]-4-[[1-oxo-4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

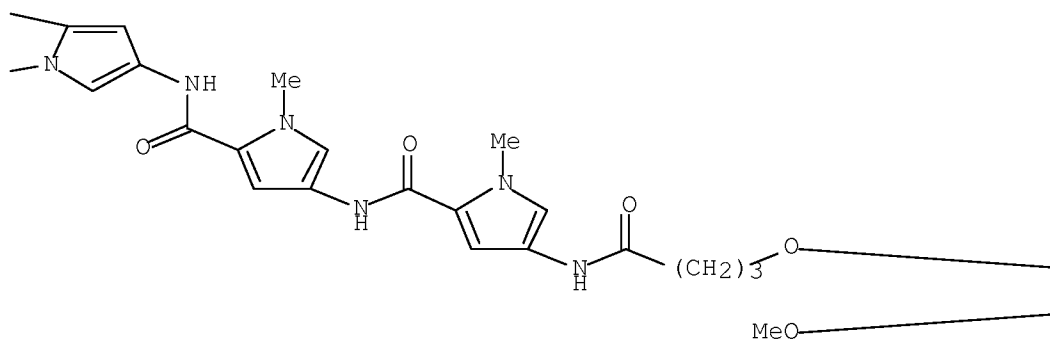
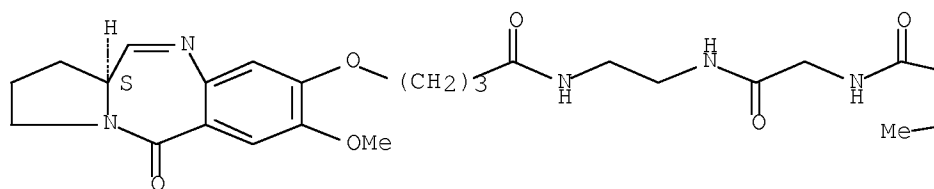


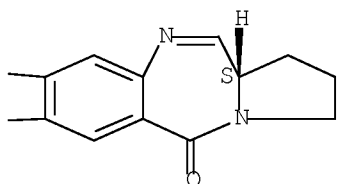


RN 861960-18-1 CAPLUS

CN 1H-Pyrrole-2-carboxamide, 1-methyl-N-[1-methyl-5-[[[2-oxo-2-[[2-[[1-oxo-4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]ethyl]amino]ethyl]amino]carbonyl]-1H-pyrrol-3-yl]-4-[[[1-methyl-4-[[1-oxo-4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]-1H-pyrrol-2-yl]carbonyl]amino]- (CA INDEX NAME)

Absolute stereochemistry.

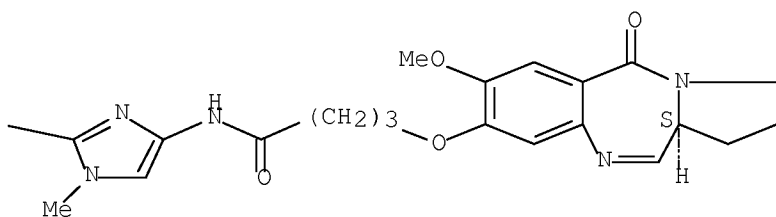
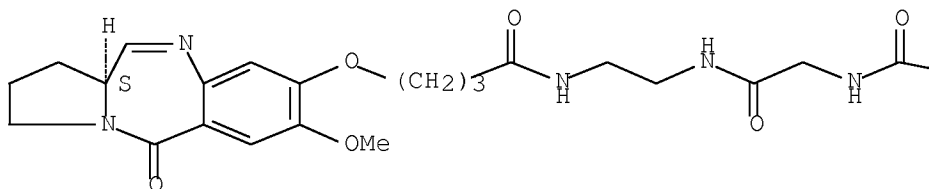




RN 861960-19-2 CAPLUS

CN 1H-Imidazole-2-carboxamide, 1-methyl-N-[2-oxo-2-[[2-[[1-oxo-4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]ethyl]amino]ethyl]-4-[[1-oxo-4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]- (CA INDEX NAME)

Absolute stereochemistry.



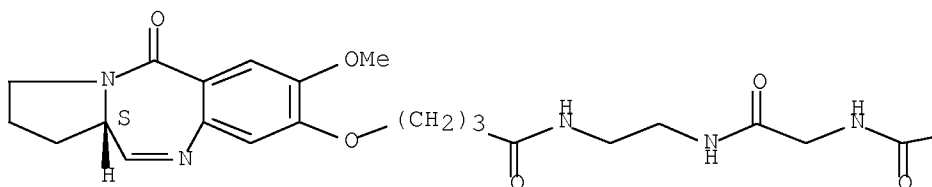
RN 861960-20-5 CAPLUS

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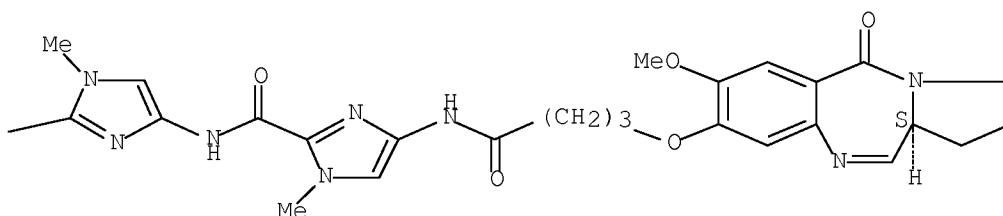
4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]ethyl]amino]ethyl]amino]carbonyl]-1H-imidazol-4-yl]-4-[[[1-oxo-4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

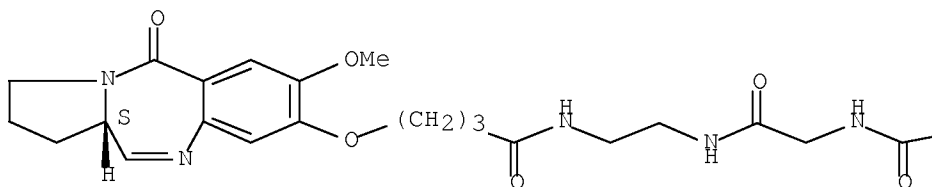


RN 861960-21-6 CAPLUS

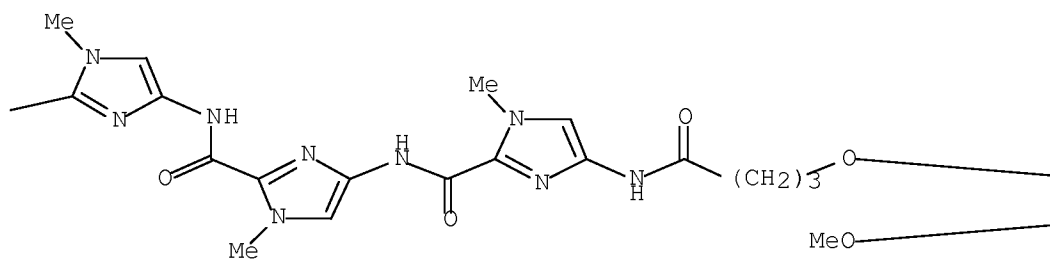
CN 1H-Imidazole-2-carboxamide, 1-methyl-N-[1-methyl-2-[[[2-oxo-2-[[2-[[1-oxo-4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]ethyl]amino]ethyl]amino]carbonyl]-1H-imidazol-4-yl]-4-[[[1-methyl-4-[[1-oxo-4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butyl]amino]-1H-imidazol-2-yl]carbonyl]amino]- (CA INDEX NAME)

Absolute stereochemistry.

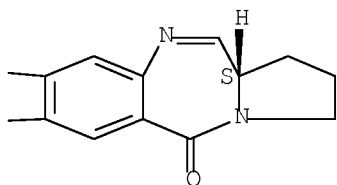
PAGE 1-A



PAGE 1-B



PAGE 1-C



RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 38 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:409522 CAPLUS Full-text

DN 142:463770

TI Preparation, DNA crosslinking reactivity and antitumor activity of pyrrolobenzodiazepines

IN Howard, Philip Wilson; Thurston, David Edwin; Gregson, Stephen John

PA Spirogen Limited, UK

SO PCT Int. Appl., 24 pp.

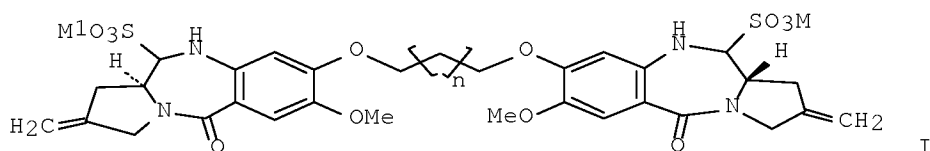
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 2005042535	A1	20050512	WO 2004-GB4497	20041022
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 20060270661	A1	20061130	US 2005-129207	20050513
	US 7244724	B2	20070717		
	US 20080039448	A1	20080214	US 2006-336623	20060120
PRAI	US 2003-513751P	P	20031022		
	GB 2004-16511	A	20040723		
	WO 2004-GB4497	A1	20041022		
	US 2005-129207	A1	20050513		
OS	MARPAT 142:463770				
GI					



AB The present invention discloses preparation of pyrrolobenzodiazepine derivs., such as I [n = 1 to 10; M, M1 = monovalent pharmaceutically acceptable cation; M and M1 together = divalent pharmaceutically acceptable cation], or solvate thereof, in the manufacture of a medicament for the treatment of a gene-based disease. Thus, I [n = 1; M, M1 = Na (II)] prepared by adding an aqueous solution of sodium sulfite to a stirred solution I [n = 1; M, M1 = H] in dichloromethane followed by vigorous stirring for 24 h. Pyrrolobenzodiazepine derivative II exhibited antitumor potency (IC50 less than 10 nM) against K562 human chronic myeloid leukemia cells and crosslinking reactivity [XL50 less than 50 nM].

IT 851455-96-4P, SJG 720 851455-97-5P, SJG 738

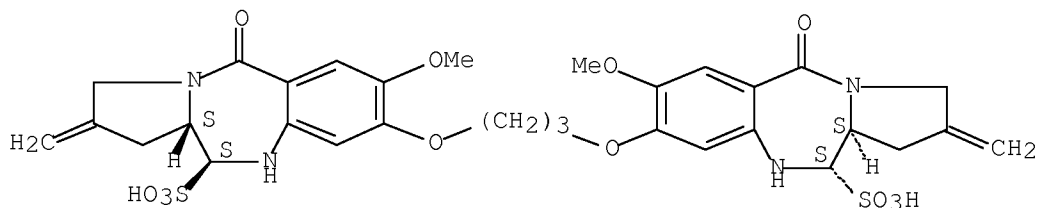
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation, DNA crosslinking reactivity and cytotoxicity of pyrrolobenzodiazepines)

RN 851455-96-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-11-sulfonic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,5,10,11,11a-hexahydro-7-methoxy-2-methylene-5-oxo-, disodium salt, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

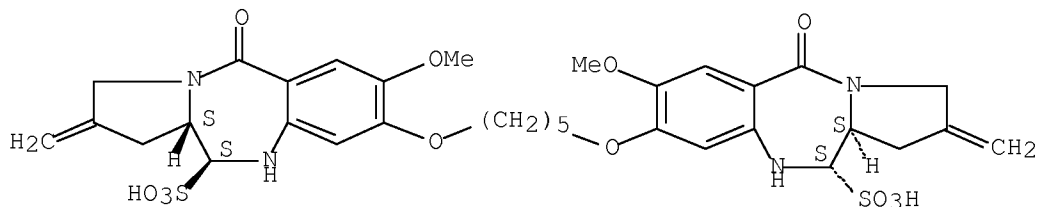


● 2 Na

RN 851455-97-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-11-sulfonic acid, 8,8'-[1,5-pentanediybis(oxy)]bis[2,3,5,10,11,11a-hexahydro-7-methoxy-2-methylene-5-oxo-, disodium salt, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



● 2 Na

IT 232931-57-6, SJG-136 260417-62-7, DRG 16

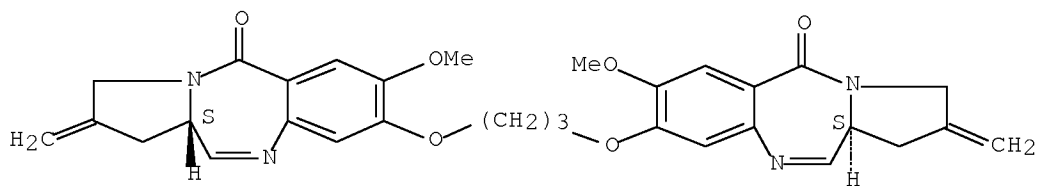
RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation, DNA crosslinking reactivity and cytotoxicity of pyrrolobenzodiazepines)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

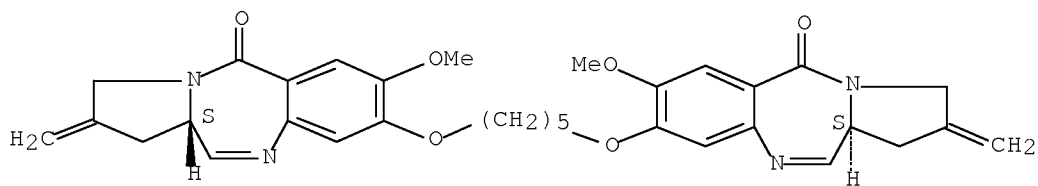
Absolute stereochemistry. Rotation (+).



RN 260417-62-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediy]bis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



L18 ANSWER 39 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:395315 CAPLUS Full-text  
 DN 142:447059  
 TI Method for preparation of pyrrolobenzodiazepine derivatives and  
 compositions comprising them  
 IN Vishnuvajjala, B. Rao; Liu, Paul S.; Snader, Kenneth M.; Thurston, David;  
 Howard, Philip W.; Turner, Gregory  
 PA Government of the United States of America, Represented by the Secretary  
 Department of Health and Human Services, USA; Spirogen, Ltd.; Starks  
 Associates, Inc.; Midwest Research Institute; Hsiao, Luke Y.  
 SO PCT Int. Appl., 89 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005040170	A2	20050506	WO 2004-US35050	20041022
	WO 2005040170	A3	20050630		
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	RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	AU 2004284075	A1	20050506	AU 2004-284075	20041022
	CA 2543318	A1	20050506	CA 2004-2543318	20041022
	EP 1675857	A2	20060705	EP 2004-817338	20041022
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR			
	US 20070072846	A1	20070329	US 2006-576689	20060814
PRAI	US 2003-513751P	P	20031022		
	WO 2004-US35050	W	20041022		
OS	CASREACT 142:447059; MARPAT 142:447059				
GI					

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Disclosed is: compds. I [X = OH, ether, silyl ether, trialkylsilyl ether, ester, carbonate, (cyclic) carbamate, (cyclic) thiocarbamate, OAc, SH, sulfide, sulfoxide, sulfone, sulfite, bisulfite, sulfonamide, amine, amide, N3, CN, halogen, triphenylphosphonium, silyl, trialkylsilyl, amino acid, phosphorus-containing group; Y = H, X; R1, R2 = H, C1-8-alkyl, aryl, heterocycle; R3, R4, R8 = H, (un)substituted C1-24-alkyl, C2-24-alkenyl, C2-24-alkynyl, (un)substituted aryl; R5, R6 = H, C1-8-alkyl, aryl, heterocycle; R7 = H, absent; T1, T2 = O, S, NR8; Z = divalent radical of (un)substituted alkane, alkene, alkyne (optionally containing a heteroatom or a carbonyl); p =  $\geq 2$ ; with the proviso that when dashed line from CY to NR7 is a double bond, R7 is absent & Y = H and with dashed line is a single bond R7 = H & Y = X; with the proviso that when the dashed line to R1 is a double bond, then R2 is absent; with the proviso that when the dashed line to R5 is a double bond, then R6 is absent] or a salt thereof, wherein the compound is a solid. Also

disclosed are: a pharmaceutical composition comprising a compound I and a carrier; a method of inhibiting growth of a cell, which method comprises administering in an amount effective to inhibit growth a compound I; a method of treating cancer in a mammal, which method comprises administering in an amount effective to treat cancer a compound I; a method of treating a viral, parasitic, or bacterial infection of a cell, which method comprises administering in an amount effective to treat a viral, parasitic, or bacterial infection a compound I; and a method of preparing a compound I as described herein. The method of preparation of I comprises: (a) providing a compound II; and (b) reaction II with a nucleophile, e.g. water, an alc., a thiol or an amine, to give the crystalline solid I. Thus, dimer III [A = (CH<sub>2</sub>)<sub>3</sub>] was prepared from 4-HO-3-MeOC<sub>6</sub>H<sub>3</sub>CO<sub>2</sub>Me and trans-4-hydroxy-L-proline via coupling of diacid IV [A = (CH<sub>2</sub>)<sub>3</sub>] with trans-4-hydroxy-L-prolinol derivative V [TBDMS = SiMe<sub>2</sub>CMe<sub>3</sub>] and oxidative cyclization of bisamide VI [A = (CH<sub>2</sub>)<sub>3</sub>]. The in vitro antitumor activity of III [A = (CH<sub>2</sub>)<sub>3</sub>] was determined [LC<sub>50</sub> = 28.2 nM vs. leukemia cell line HL-60(TB); LC<sub>50</sub> = 67.6 nM vs. non-small cell lung cell line NCI-H23; LC<sub>50</sub> = 251.2 nM vs. colon cell line COLO 205; LC<sub>50</sub> = 467.7 nM vs. CNS cell line SNB-75; LC<sub>50</sub> = 7.1 nM vs. melanoma cell line UACC-62; LC<sub>50</sub> = 1000 nM vs. ovarian cell line SK-OV-3; LC<sub>50</sub> = 1000 nM vs. renal cell line CAKI-1; LC<sub>50</sub> = 1000 nM vs. prostate cell line DU-145; LC<sub>50</sub> = 57.5 nM vs. breast cell line MDA-N].

IT 232931-57-6

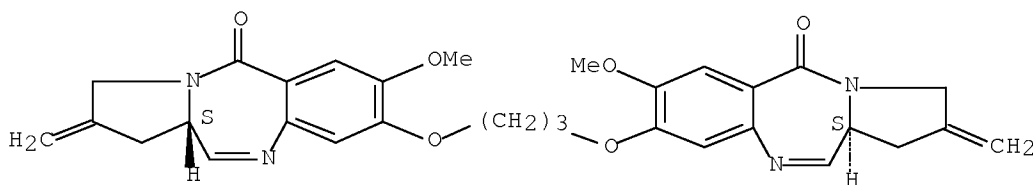
RL: RCT (Reactant); RACT (Reactant or reagent)

(nucleophilic addition reactions of, with alcs., thiols and amines;  
preparation  
of pyrrolobenzodiazepine derivs. as antitumor antibiotics and other  
medicinals)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 232931-64-5P

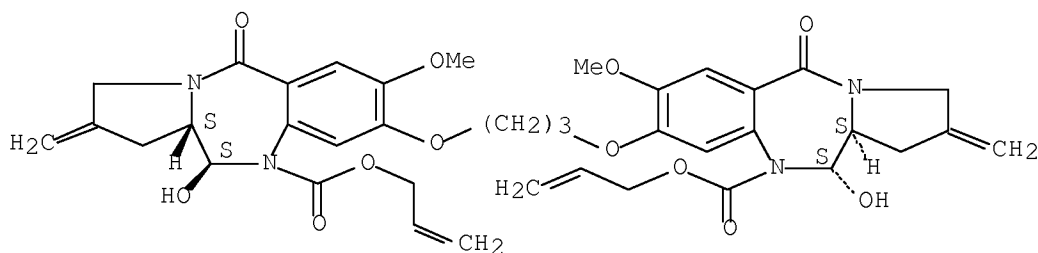
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and N-decarbonylation of; preparation of pyrrolobenzodiazepine derivs. as antitumor antibiotics and other medicinals)

RN 232931-64-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 851177-99-6P 851178-00-2P 851178-01-3P  
 851178-02-4P 851178-03-5P 851178-04-6P  
 851178-05-7P 851178-06-8P 851178-07-9P  
 851178-08-0P 851178-09-1P 851178-10-4P  
 851178-11-5P 851178-12-6P 851178-13-7P  
 851178-14-8P 851178-15-9P 851178-16-0P  
 851178-17-1P

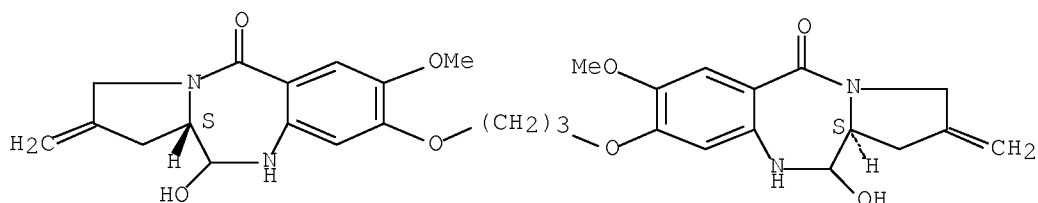
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
 (Uses)

(preparation of pyrrolobenzodiazepine derivs. as antitumor antibiotics and  
 other medicinals)

RN 851177-99-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
 propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-11-hydroxy-7-methoxy-2-  
 methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

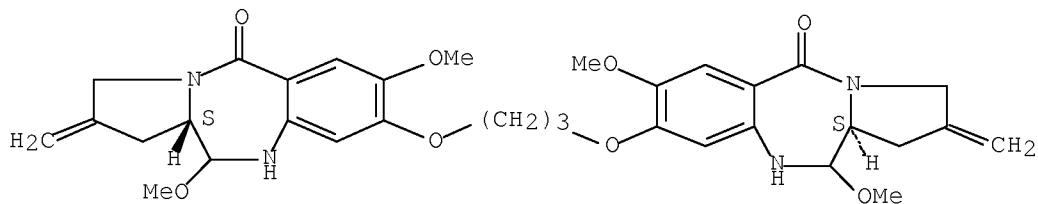
Absolute stereochemistry.



RN 851178-00-2 CAPLUS

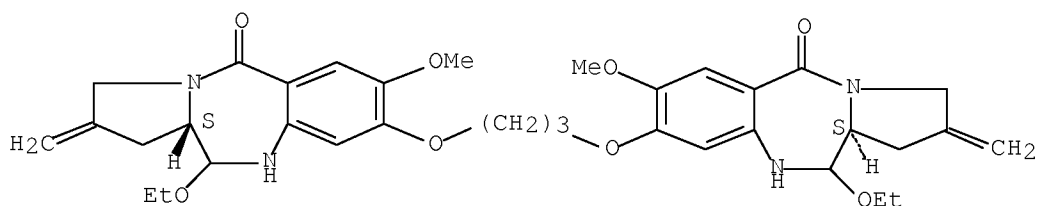
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
 propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7,11-dimethoxy-2-  
 methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



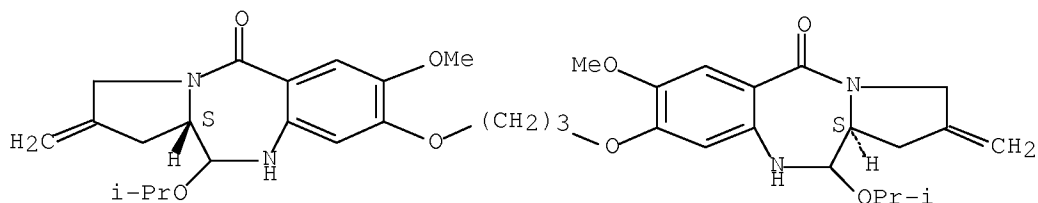
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Absolute stereochemistry.



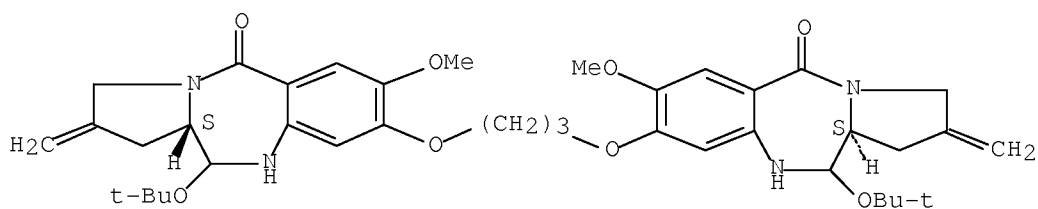
RN 851178-02-4 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-11-(1-methylethoxy)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 851178-03-5 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[11-(1,1-dimethylethoxy)-1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

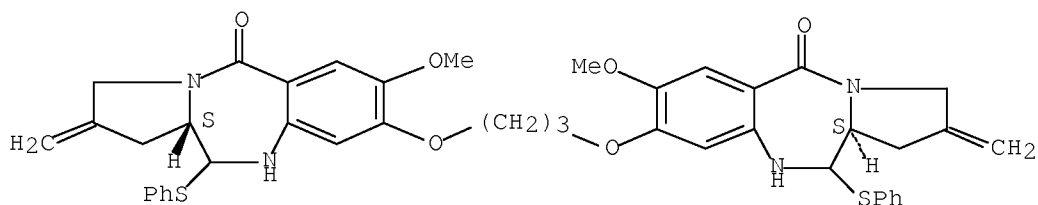
Absolute stereochemistry.



RN 851178-04-6 CAPLUS  
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propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-11-(phenylthio)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

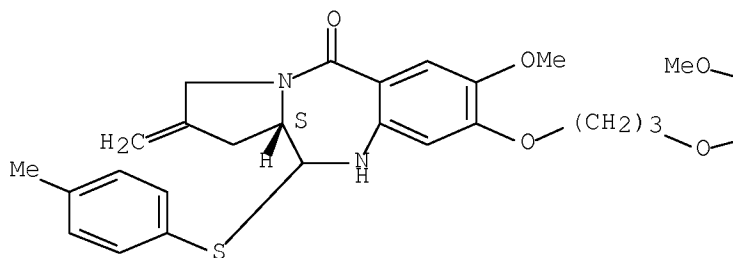


RN 851178-05-7 CAPLUS

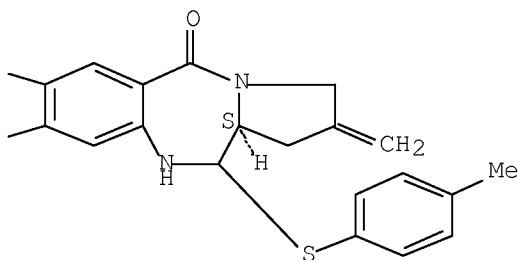
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-11-[(4-methylphenyl)thio]-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

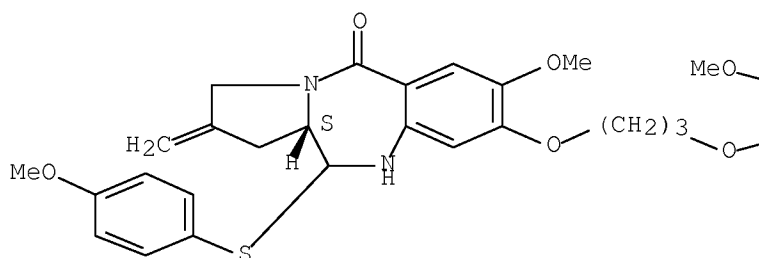


RN 851178-06-8 CAPLUS

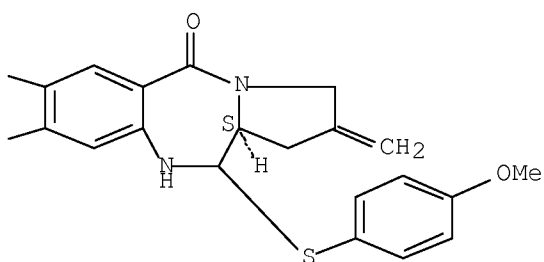
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-bis(methoxy)propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-11-[(4-methoxyphenyl)thio]-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



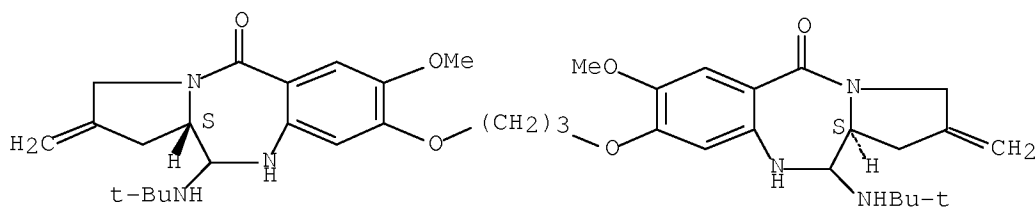
PAGE 1-B



RN 851178-07-9 CAPLUS

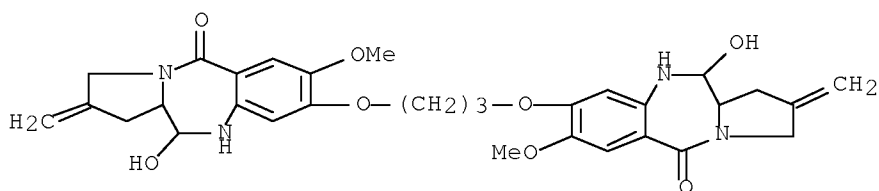
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[11-[(1,1-dimethylethyl)amino]-1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



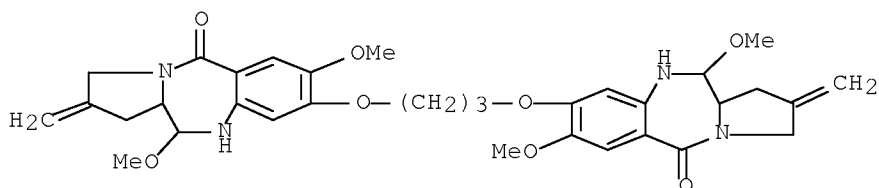
RN 851178-08-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-11-hydroxy-7-methoxy-2-methylene- (9CI) (CA INDEX NAME)



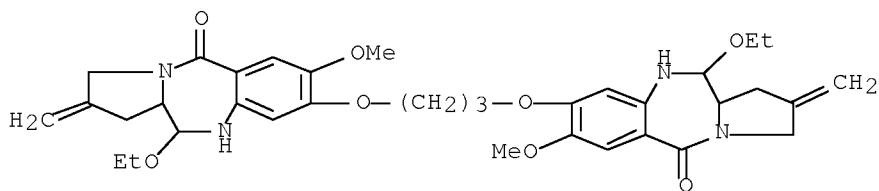
RN 851178-09-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7,11-dimethoxy-2-methylene- (9CI) (CA INDEX NAME)



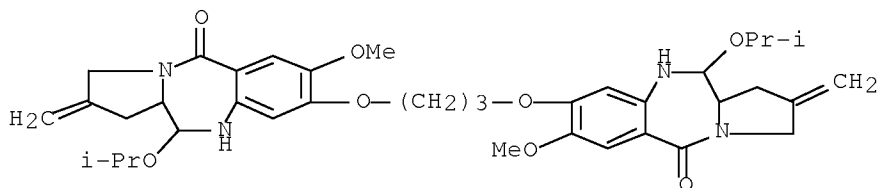
RN 851178-10-4 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[11-ethoxy-1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene- (9CI) (CA INDEX NAME)

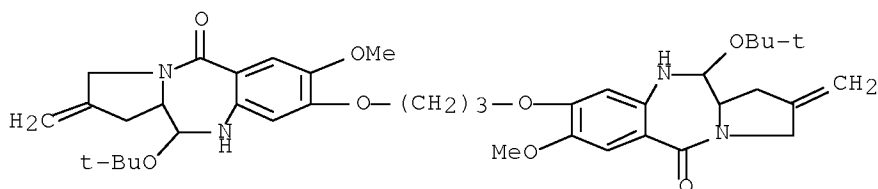


RN 851178-11-5 CAPLUS

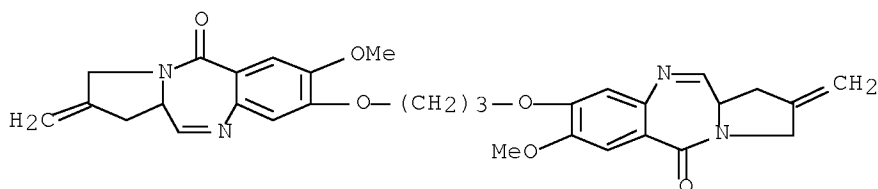
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-11-(1-methylethoxy)- (9CI) (CA INDEX NAME)



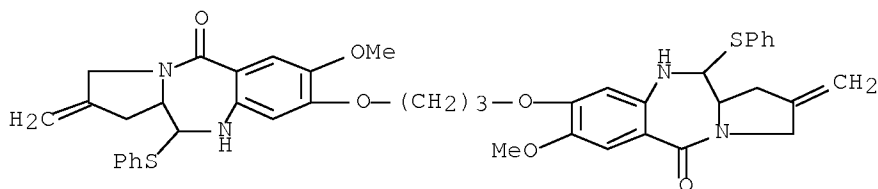
RN 851178-12-6 CAPLUS  
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RN 851178-13-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene- (9CI) (CA INDEX NAME)

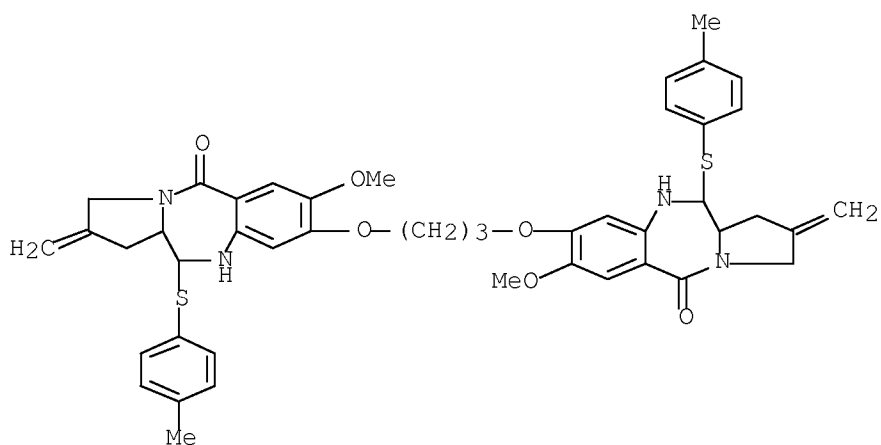


RN 851178-14-8 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-11-(phenylthio)- (9CI) (CA INDEX NAME)



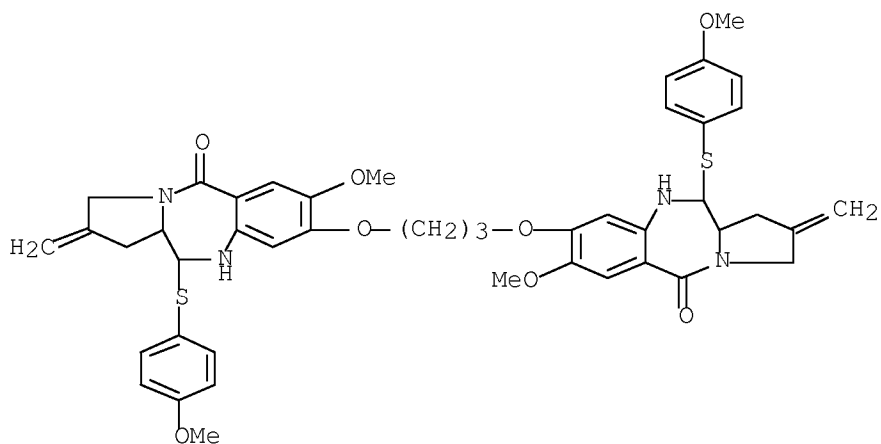
RN 851178-15-9 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-11-[(4-methylphenyl)thio]- (9CI) (CA INDEX NAME)





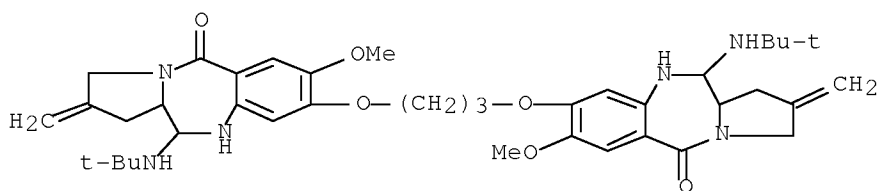
RN 851178-16-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-11-[(4-methoxyphenyl)thio]-2-methylene- (9CI) (CA INDEX NAME)



RN 851178-17-1 CAPLUS

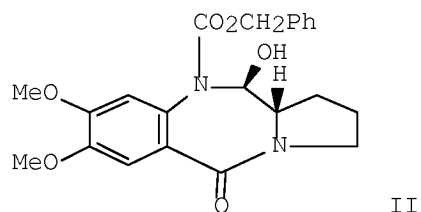
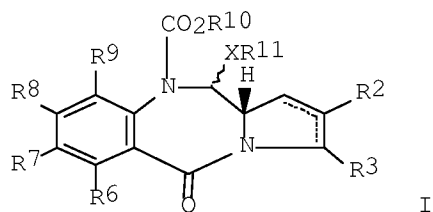
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[11-[(1,1-dimethylethyl)amino]-1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene- (9CI) (CA INDEX NAME)





L18 ANSWER 40 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:238991 CAPLUS Full-text  
 DN 142:316867  
 TI Synthesis of protected pyrrolobenzodiazepines  
 IN Howard, Philip; Masterson, Luke  
 PA Spirogen Limited, UK  
 SO PCT Int. Appl., 120 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005023814	A1	20050317	WO 2004-GB3873	20040910
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
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	EP 1664049	A1	20060607	EP 2004-768420	20040910
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK			
	IN 2006DN01149	A	20070810	IN 2006-DN1149	20060303
	US 20060264622	A1	20061123	US 2006-571274	20060309
PRAI	GB 2003-21295	A	20030911		
	WO 2004-GB3873	W	20040910		
OS	CASREACT 142:316867; MARPAT 142:316867				
GI					



AB Pyrrolobenzodiazepines I [R2, R3 = H, O, OH, CH2, CN, R, OR, O3SR, COR; R = (un)substituted alkyl, heterocyclyl, aryl; R6, R7, R9 = H, R, OH, OR, SH, SR, NH2, NHR, NRR1, NO2, SnMe3, halogen; R1 = (un)substituted alkyl, heterocyclyl, aryl; R8 = H, R, OH, OR, SH, SR, NH2, NHR, NRR1, NO2, SnMe3, halogen, XR4X; R4 = alkylene, heteroalkylene; X = O, S, NH; CO2R10 = protective group; R11 = H, R] were prepared by treating an isocyanatobenzoate with an alc. to form the carbamate, followed by (S)-2-pyrrolidinemethanol, cyclizing, optionally alkylating the resulting OH group. Thus, 2,4,5-O2N(MeO)2C6H2CO2H was amidated with (S)-2-pyrrolidinemethanol, followed by tert-butyldimethylsilyl protection, reduction of the nitro group, and conversion of the amine to isocyanate. The isocyanate was treated with benzyl alc. to give the benzyloxycarbonylamine which was desilylated and cyclized with base to give the pyrrolobenzodiazepine II.

IT 848004-77-3F 848004-82-0F 848004-83-1F

848004-84-2F

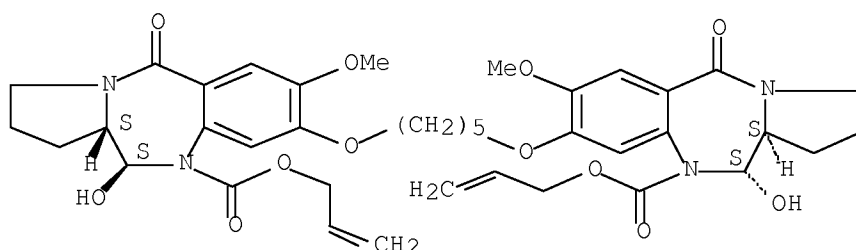
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of protected pyrrolobenzodiazepines)

RN 848004-77-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediy]bis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

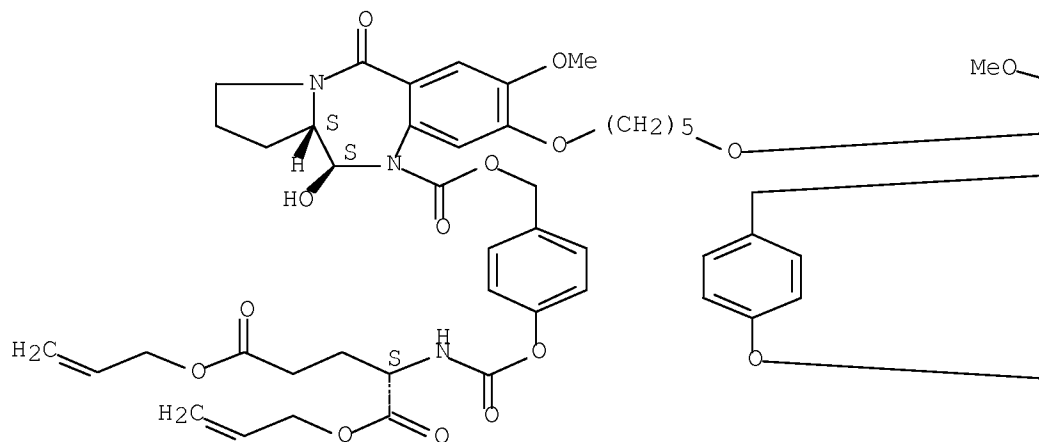


RN 848004-82-0 CAPLUS

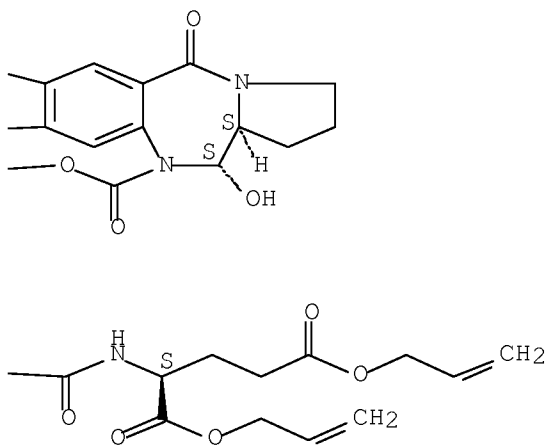
CN L-Glutamic acid, N,N'-[1,5-pentanediy]bis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneoxycarbonyl]]bis-, tetra-2-propenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



PAGE 1-B

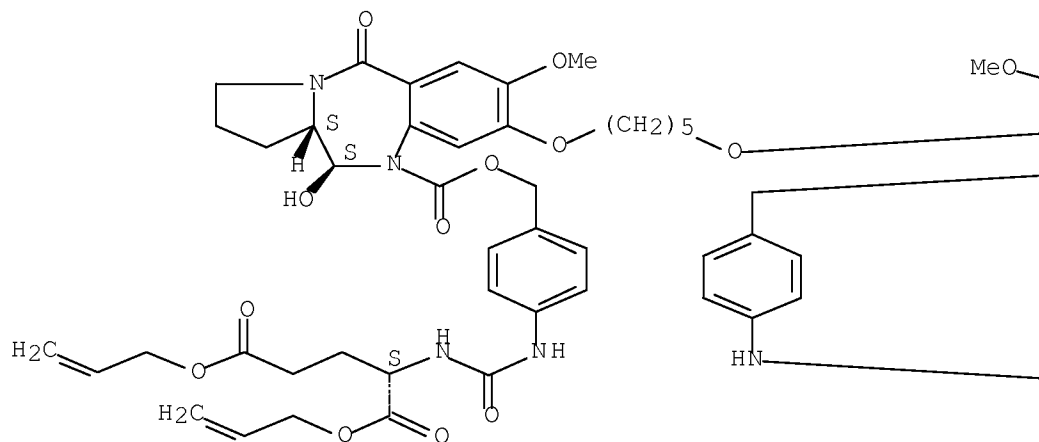


RN 848004-83-1 CAPLUS

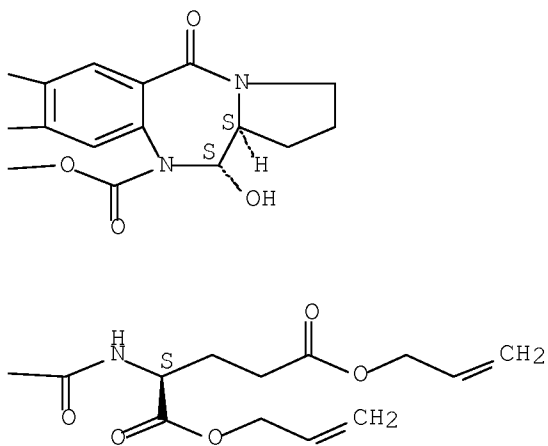
CN L-Glutamic acid, N,N'-[1,5-pentanediy]bis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneiminocarbonyl]]bis-, tetra-2-propenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



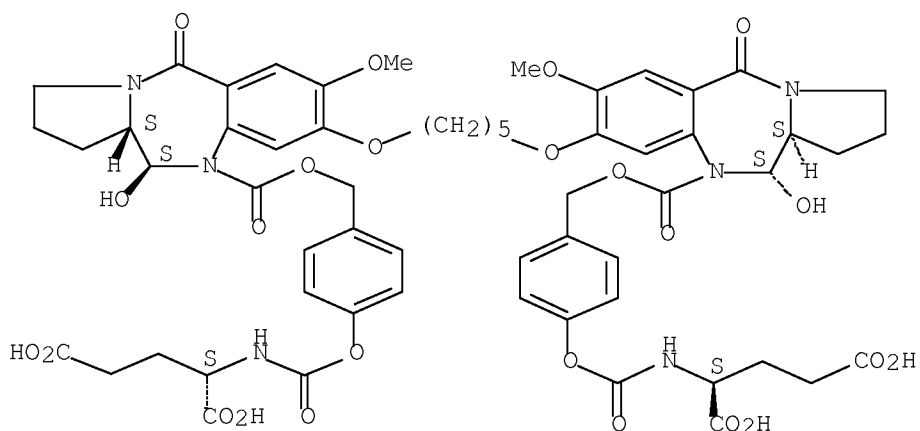
PAGE 1-B



RN 848004-84-2 CAPLUS

CN L-Glutamic acid, N,N'-[1,5-pentanediyldis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneoxycarbonyl]]bis- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



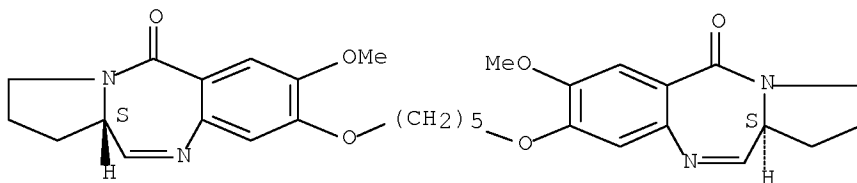
IT 145325-57-1P 848004-85-3P 848005-10-7P  
848005-11-8P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of protected pyrrolobenzodiazepines)

RN 145325-57-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediyldis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
(CA INDEX NAME)

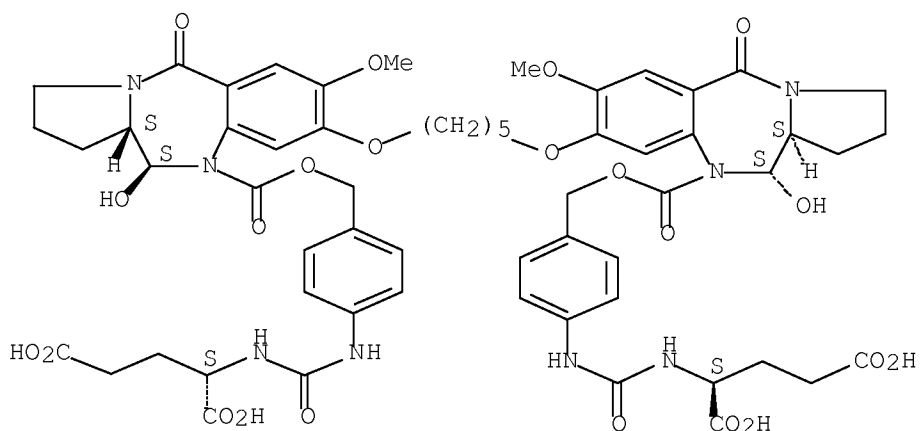
Absolute stereochemistry. Rotation (+).



RN 848004-85-3 CAPLUS

CN L-Glutamic acid, N,N'-[1,5-pentanediyldis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneiminocarbonyl]]bis- (9CI)  
(CA INDEX NAME)

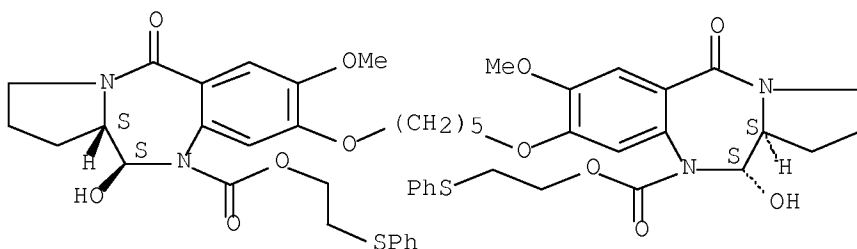
Absolute stereochemistry. Rotation (+).



RN 848005-10-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,5-pentanediy]bis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
methoxy-5-oxo-, bis[2-(phenylthio)ethyl] ester, (11S,11'S,11aS,11'aS)-  
(9CI) (CA INDEX NAME)

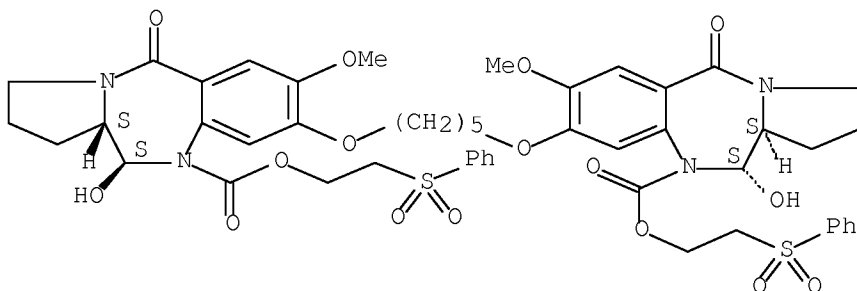
Absolute stereochemistry. Rotation (+).



RN 848005-11-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,5-pentanediy]bis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
methoxy-5-oxo-, bis[2-(phenylsulfonyl)ethyl] ester, (11S,11'S,11aS,11'aS)-  
(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

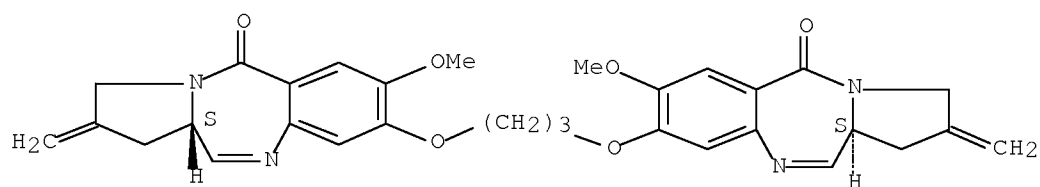




RE.CNT 3      THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

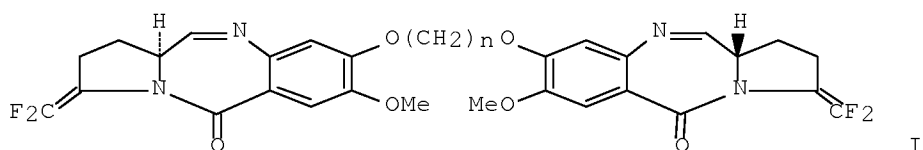
L18 ANSWER 41 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:142547 CAPLUS Full-text  
 DN 142:405382  
 TI Sequence-Selective Interaction of the Minor-Groove Interstrand  
 Cross-Linking Agent SJG-136 with Naked and Cellular DNA: Footprinting and  
 Enzyme Inhibition Studies  
 AU Martin, Chris; Ellis, Tom; McGurk, Claire J.; Jenkins, Terence C.;  
 Hartley, John A.; Waring, Michael J.; Thurston, David E.  
 CS Department of Pharmacology, University of Cambridge, Cambridge, CB2 1PD,  
 UK  
 SO Biochemistry (2005), 44(11), 4135-4147  
 CODEN: BICHAW; ISSN: 0006-2960  
 PB American Chemical Society  
 DT Journal  
 LA English  
 AB SJG-136 (3) is a novel pyrrolobenzodiazepine (PBD) dimer that is predicted  
 from mol. models to bind in the minor groove of DNA and to form sequence-  
 selective interstrand cross-links at 5'-Pu-GATC-Py-3' (Pu = purine; Py =  
 pyrimidine) sites through covalent bonding between each PBD unit and guanines  
 on opposing strands. Footprinting studies have confirmed that high-affinity  
 adducts do form at 5'-G-GATC-C-3' sequences and that these can inhibit RNA  
 polymerase in a sequence-selective manner. At higher concns. of SJG-136, bands  
 that migrate more slowly than one of the 5'-G-GATC-C-3' footprint sites show  
 significantly reduced intensity, concomitant with the appearance of higher  
 mol. weight material near the gel origin. This phenomenon is attributed to  
 interstrand crosslinking at the 5'-G-GATC-C-3' site and is the first report of  
 DNA footprinting being used to detect interstrand cross-linked adducts. The  
 control dimer GD113 (4), of similar structure to SJG-136 but unable to cross-  
 link DNA due to its C7/C7'-linkage rather than C8/C8'-linkage, neither  
 produces footprints with the same DNA sequence nor blocks transcription at  
 comparable concns. In addition to the two high-affinity 5'-G-GATC-C-3'  
 footprints on the MS2 DNA sequence, other SJG-136 adducts of lower affinity  
 are observed that can still block transcription but with lower efficiency.  
 All these sites contain the 5'-GXXC-3' motif (where XX includes AG, TA, GC,  
 CT, TT, GG, and TC) and represent less-favored cross-link sites. In time-  
 course expts., SJG-136 blocks transcription if incubated with a double-  
 stranded DNA template before the transcription components are added; addition  
 after transcription is initiated fails to elicit blockage. Single-strand  
 ligation PCR studies on a sequence from the c-jun gene show that SJG-136 binds  
 to 5'-GAAC-3'/5'-GTTC-3' (preferred) or 5'-GAGC-3'/5'-GCTC-3' sequences.  
 Significantly, adducts are obtained at the same sequences following extraction  
 of DNA from drug-treated K562 cells, confirming that the agent reaches the  
 cellular genome and interacts with the DNA in a sequence-selective fashion.  
 Finally, SJG-136 efficiently inhibits the action of restriction endonuclease  
 BglII, which has a 5'-A-GATC-T-3' motif at its cleavage site.  
 IT 232931-57-6, SJG-136  
 RL: BSU (Biological study, unclassified); DMA (Drug mechanism of action);  
 PEP (Physical, engineering or chemical process); PYP (Physical process);  
 BIOL (Biological study); PROC (Process)  
 (sequence-selective interaction of minor-groove interstrand  
 crosslinking agent SJG-136 with naked and cellular DNA, footprinting  
 and enzyme inhibition studies)  
 RN 232931-57-6 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
 propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-,  
 (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



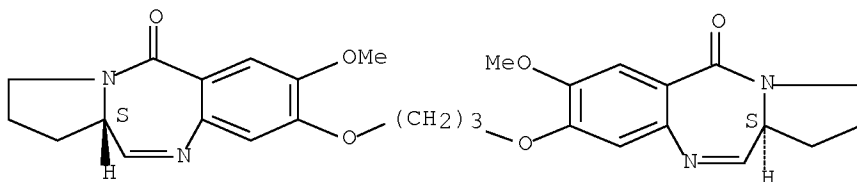
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 42 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2004:863131 CAPLUS Full-text  
 DN 142:56263  
 TI Synthesis of fluorinated analogues of SJG-136 and their DNA-binding potential  
 AU Kamal, Ahmed; Reddy, P. S. M. M.; Reddy, D. Rajasekhar; Laxman, E.; Murthy, Y. L. N.  
 CS Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad, 500007, India  
 SO Bioorganic & Medicinal Chemistry Letters (2004), 14(22), 5699-5702  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier B.V.  
 DT Journal  
 LA English  
 OS CASREACT 142:56263  
 GI



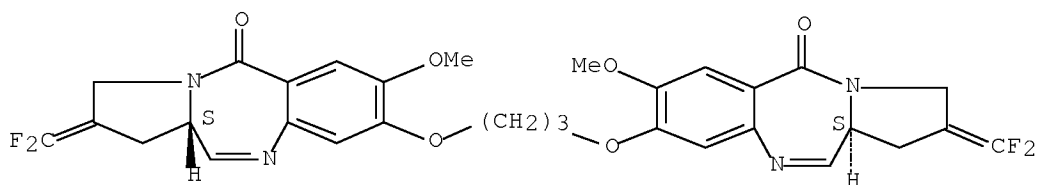
AB A series of fluorinated pyrrolobenzodiazepines I [n = 3-5] have been synthesized and exhibit remarkable DNA-binding affinity.  
 IT 140676-21-7P 808154-57-6P 808154-60-1P  
 808154-64-5P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (preparation and DNA-binding potential of  
 alkylenoxybis(difluoromethylenepyr  
 rolobenzodiazepines))  
 RN 140676-21-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 808154-57-6 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[2-(difluoromethylene)-1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

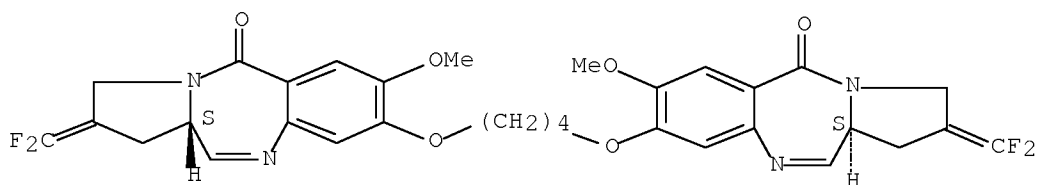
Absolute stereochemistry.



RN 808154-60-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[2-(difluoromethylene)-1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

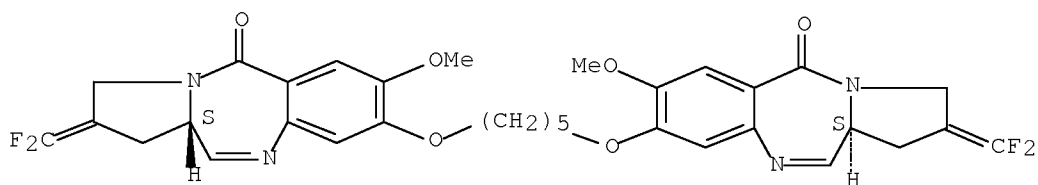
Absolute stereochemistry.



RN 808154-64-5 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanedylbis(oxy)]bis[2-(difluoromethylene)-1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

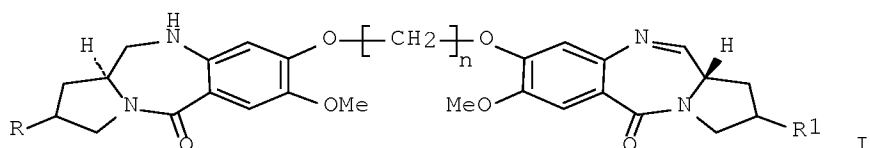
Absolute stereochemistry.



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 43 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2004:803932 CAPLUS Full-text  
 DN 141:295775  
 TI Preparation of non-cross-linking pyrrolo[2,1-c][1,4]benzodiazepines as  
 antitumor agents  
 IN Kamal, Ahmed; Ramesh, Gujjar; Srinivas, Olepu; Ramulu, Poddutoori  
 PA Council of Scientific and Industrial Research, India  
 SO U.S. Pat. Appl. Publ., 13 pp.  
 CODEN: USXXCO  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 20040192679	A1	20040930	US 2003-401782	20030331
	US 6884799	B2	20050426		
	CA 2520898	A1	20041014	CA 2003-2520898	20030331
	WO 2004087717	A1	20041014	WO 2003-IB1182	20030331
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003215821	A1	20041025	AU 2003-215821	20030331
	EP 1608664	A1	20051228	EP 2003-816509	20030331
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	RU 2314309	C2	20080110	RU 2005-133443	20030331
	IN 2004DN03250	A	20070525	IN 2004-DN3250	20041020
PRAI	US 2003-401782	A	20030331		
	WO 2003-IB1182	W	20030331		
OS	CASREACT 141:295775; MARPAT 141:295775				
GI					



AB The present invention relates to novel pyrrolo[2,1-c][1,4]benzodiazepines compds. of formula I [R, R1 = H, OH; n = 3-5], which are useful as potential antitumor agents and a process of preparing these compds. Particularly the present invention provides a process for the preparation of 7-methoxy-8-{n-[7-methoxy-(11aS)-1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5-one-8-yloxy]alkyloxy}-(11aS)-1,2,3,11a-tetrahydro- 5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one, with varying aliphatic chain length and its 2-hydroxy derivs. Two of the compds. were tested for anticancer

activity against several cell lines, which showed that a 3-carbon spacer has slightly higher activity.

IT 763125-64-0P 763125-65-1P 763125-66-2P  
763125-67-3P 763125-68-4P 763125-69-5P  
763125-71-9P 763125-72-0P 763125-73-1P

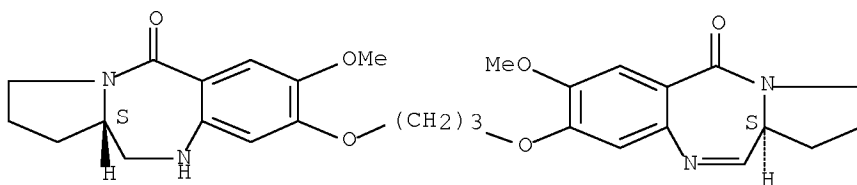
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of pyrrolobenzodiazepines as antitumor agents)

RN 763125-64-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-7-methoxy-8-[3-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (CA INDEX NAME)

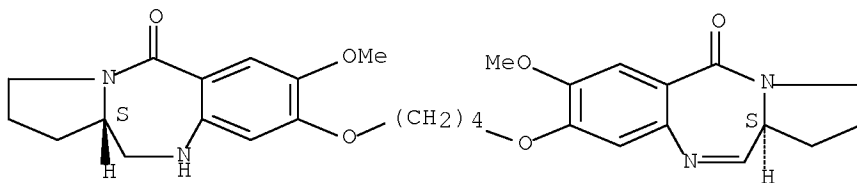
Absolute stereochemistry.



RN 763125-65-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-7-methoxy-8-[4-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (11aS)- (9CI) (CA INDEX NAME)

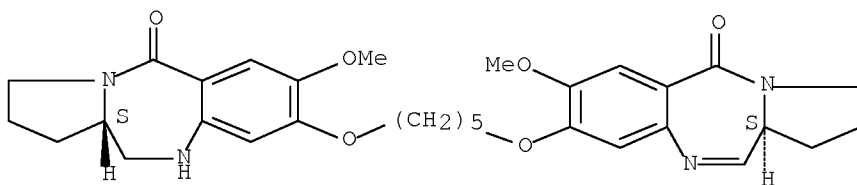
Absolute stereochemistry.



RN 763125-66-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-7-methoxy-8-[[5-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (9CI) (CA INDEX NAME)

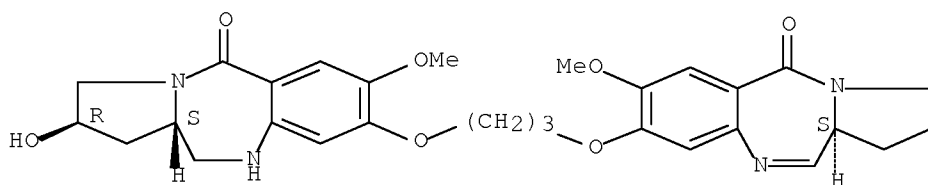
Absolute stereochemistry.



RN 763125-67-3 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-2-hydroxy-7-methoxy-8-[3-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (2R,11aS)- (CA INDEX NAME)

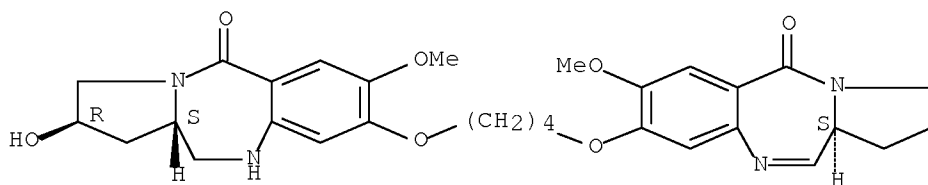
Absolute stereochemistry.



RN 763125-68-4 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-2-hydroxy-7-methoxy-8-[4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (2R,11aS)- (CA INDEX NAME)

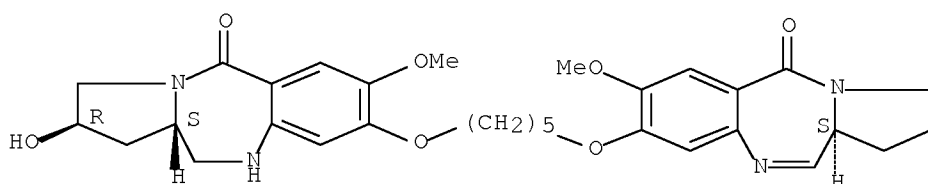
Absolute stereochemistry.



RN 763125-69-5 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-2-hydroxy-7-methoxy-8-[[5-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (2R,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



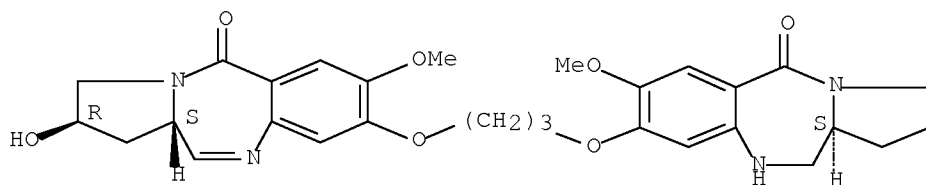
RN 763125-71-9 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8-[3-[[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-1,2,3,11a-tetrahydro-2-hydroxy-7-methoxy-, (2R,11aS)- (CA INDEX NAME)



INDEX NAME)

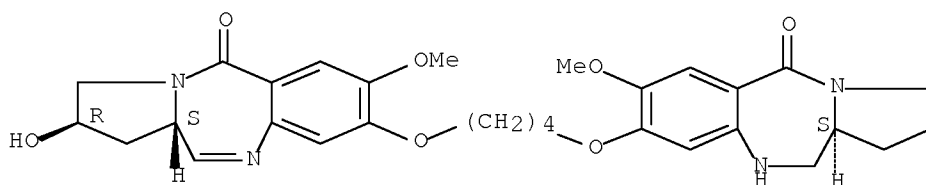
Absolute stereochemistry.



RN 763125-72-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8-[4-[[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-1,2,3,11a-tetrahydro-2-hydroxy-7-methoxy-, (2R,11aS)- (CA INDEX NAME)

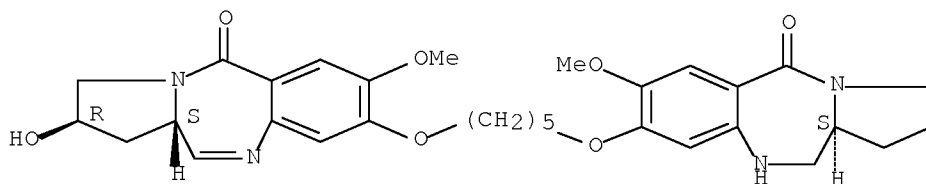
Absolute stereochemistry.



RN 763125-73-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8-[[5-[[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-1,2,3,11a-tetrahydro-2-hydroxy-7-methoxy-, (2R,11aS)- (CA INDEX NAME)

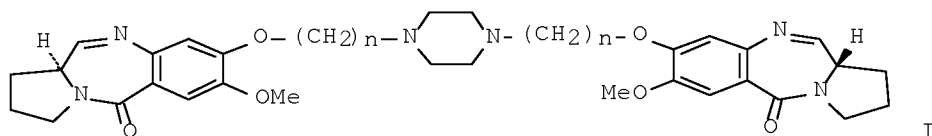
Absolute stereochemistry.



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 44 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2004:802557 CAPLUS Full-text  
 DN 141:295774  
 TI Preparation of pyrrolo[2,1-c][1,4]benzodiazepines as anticancer agents  
 IN Kamal, Ahmed; Reddy, Peram Surakattula Murali Mohan; Reddy, Depatla  
 Rajasekhar  
 PA Council of Scientific and Industrial Research, India  
 SO U.S. Pat. Appl. Publ., 12 pp.  
 CODEN: USXXCO  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 20040192678	A1	20040930	US 2003-401754	20030331
	US 7015215	B2	20060321		
	CA 2520897	A1	20041014	CA 2003-2520897	20030331
	WO 2004087716	A1	20041014	WO 2003-IB1164	20030331
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003215810	A1	20041025	AU 2003-215810	20030331
	EP 1608663	A1	20051228	EP 2003-816507	20030331
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	IN 2004DN02980	A	20070413	IN 2004-DN2980	20040930
PRAI	US 2003-401754	A	20030331		
	WO 2003-IB1164	W	20030331		
OS	CASREACT 141:295774; MARPAT 141:295774				
GI					



AB The present invention provides a process for the preparation of pyrrolo[2,1-c][1,4]benzodiazepin-5-one analogs, such as I [n = 2-10], by reacting (2S)-N-[4-hydroxy-5-methoxy-2-nitrobenzoyl]-pyrrolidine-2- carboxaldehyde di-Et thioacetal with a dibromoalkane, isolating (2S)-N-[4-(bromoalkoxy)-5-methoxy-2-nitrobenzoyl]pyrrolidine-2- carboxaldehyde di-Et thioacetal so formed and reacting the isolate with piperazine, isolating 1,1'-{[(bisalkane-1,N-diyl)piperazine]dioxo}bis[(11a S)-7-methoxy-2-nitrobenzoylpyrrolidin-2-carboxaldehyde diethylthioacetal], followed by reduction of nitro group and reacting amino compound with a deprotecting agent. The prepared pyrrolo[2,1-

c][1,4]benzodiazepines are useful as anticancer agents. Thus, I (n = 4) was prepared as described above and showed significant anticancer activity against sixty human tumor cells derived from nine cancer types (leukemia, non-small-cell lung colon, CNS, melanoma, ovarian, prostate, and breast cancer).

IT 764680-79-7F 764680-84-4F 764680-89-9P  
764680-91-3P 764680-93-5P 764680-95-7P  
764680-97-9P 764680-99-1P 764681-01-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

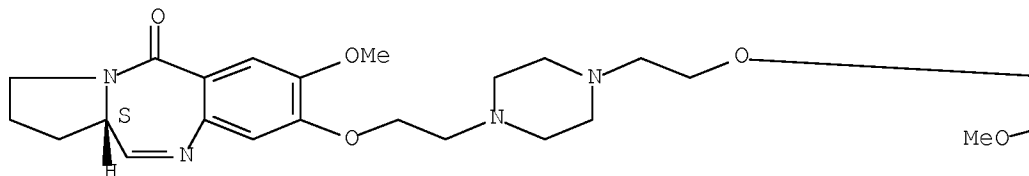
(preparation of pyrrolobenzodiazepinones as anticancer agents)

RN 764680-79-7 CAPLUS

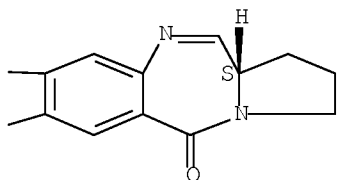
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-piperazinediylbis(2,1-ethanediylloxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

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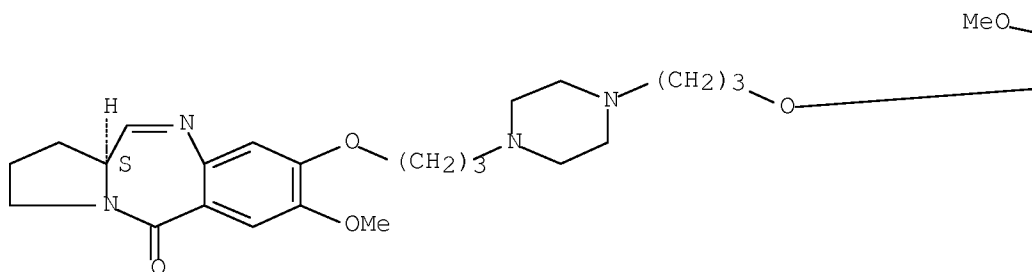


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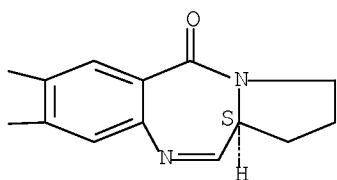
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-piperazinediylbis(3,1-propanediylloxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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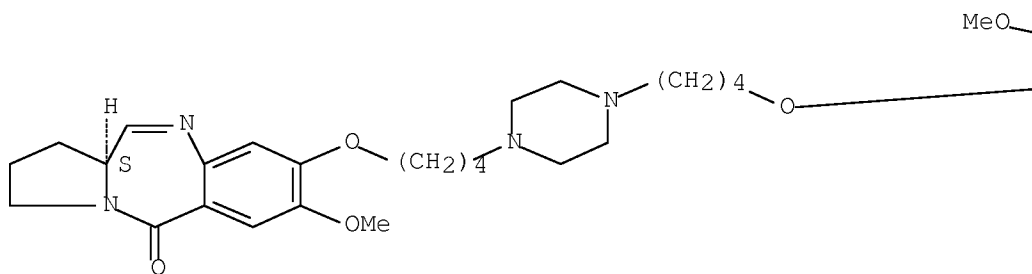


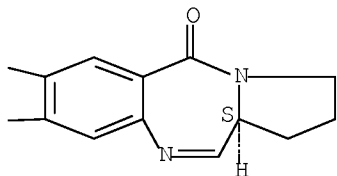
RN 764680-89-9 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-piperazinediylbis(4,1-butanediylloxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

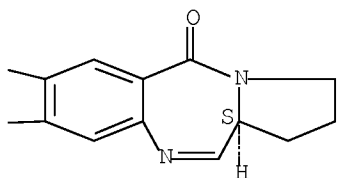
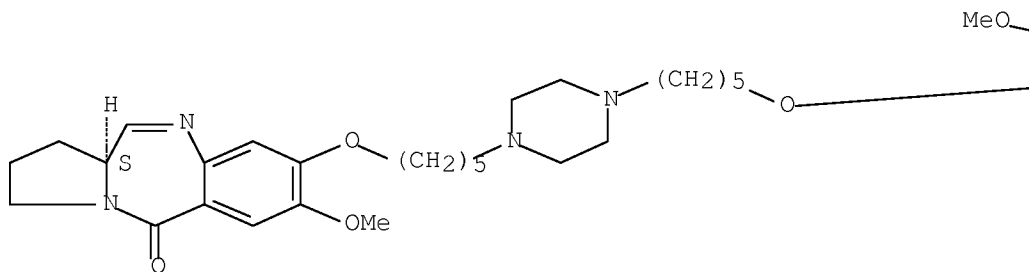




RN 764680-91-3 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-piperazinediylbis(5,1-pentanedioxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

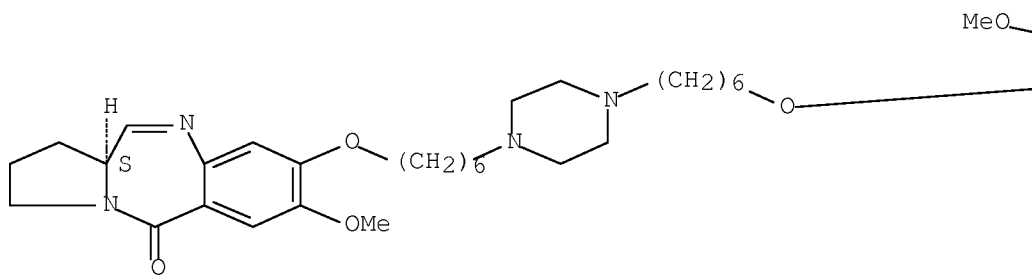


RN 764680-93-5 CAPLUS

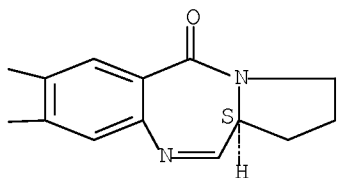
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-piperazinediylbis(6,1-hexanedioxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

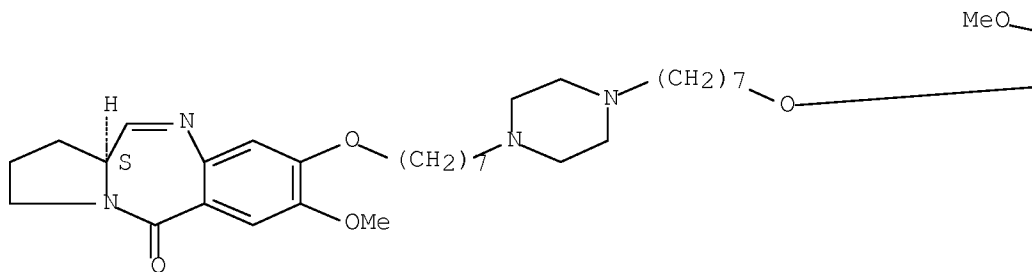


RN 764680-95-7 CAPLUS

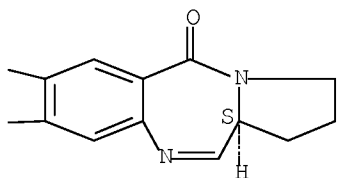
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-piperazinediylbis(7,1-heptanediylloxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

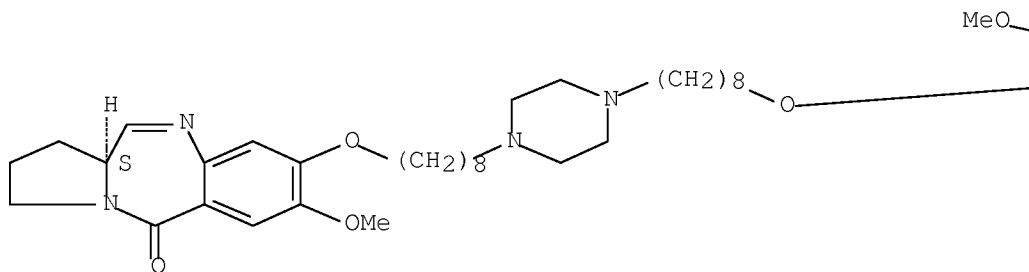


RN 764680-97-9 CAPLUS

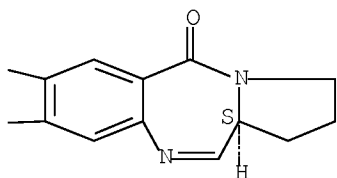
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-piperazinediylbis(8,1-octanediylloxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

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PAGE 1-B

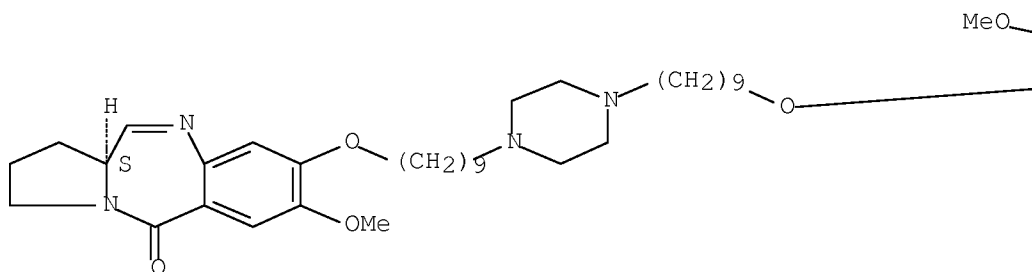


RN 764680-99-1 CAPLUS

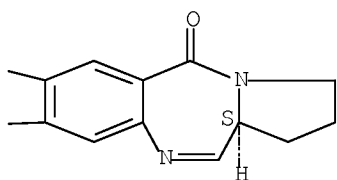
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-piperazinediylbis(9,1-nonanediylloxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



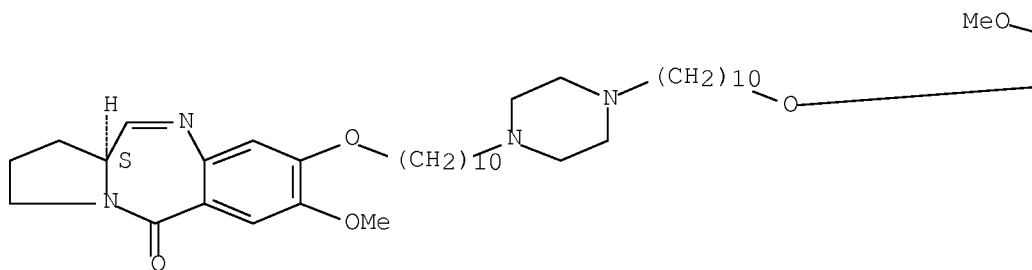
PAGE 1-B



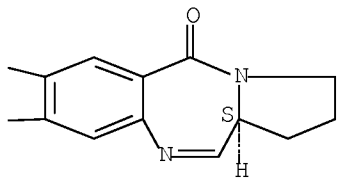
RN 764681-01-8 CAPLUS  
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-piperazinediylbis(10,1-decanediylloxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

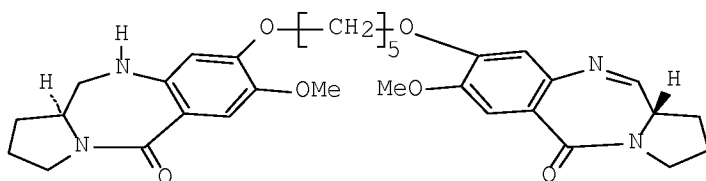






RE.CNT 3      THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

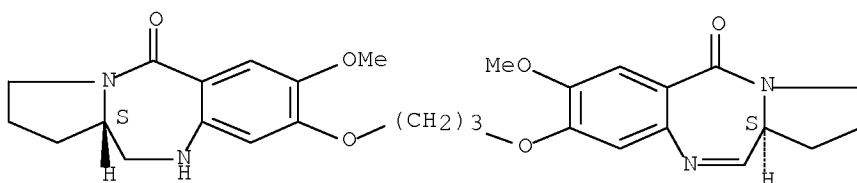
L18 ANSWER 45 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2004:791713 CAPLUS Full-text  
 DN 141:342888  
 TI Design, synthesis, and evaluation of mixed imine-amine  
 pyrrolobenzodiazepine dimers with efficient DNA binding affinity and  
 potent cytotoxicity  
 AU Kamal, Ahmed; Ramesh, G.; Srinivas, O.; Ramulu, P.; Laxman, N.; Rehana,  
 Tasneem; Deepak, M.; Achary, M. S.; Nagarajaram, H. A.  
 CS Biotransformation Laboratory, Division of Organic Chemistry, Indian  
 Institute of Chemical Technology, Hyderabad, 500 007, India  
 SO Bioorganic & Medicinal Chemistry (2004), 12(20), 5427-5436  
 CODEN: BMECEP; ISSN: 0968-0896  
 PB Elsevier Ltd.  
 DT Journal  
 LA English  
 OS CASREACT 141:342888  
 GI



I

AB Synthesis of mixed imine-amine pyrrolobenzodiazepine (PBD) dimers that are  
 comprised of DC-81 and secondary amine (N10) of DC-81 subunits tethered to  
 their C8 positions through alkanedioxy linkers (comprised of three and five  
 carbons) is described. These noncross-linking unsym. mols. exhibit  
 significant DNA minor groove binding ability and one of them I linked through  
 the pentanedioxy chain exhibits efficient DNA binding ability ( $\Delta T_m = 11.0^\circ\text{C}$ )  
 when compared to naturally occurring DC-81 ( $\Delta T_m = 0.7^\circ\text{C}$ ). The imine-amine  
 PBD dimers exhibit promising in vitro antitumor activity in a number of human  
 cancer cell lines.  
 IT 763125-64-0P 763125-66-2P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
 (Uses)  
 (pyrrolobenzodiazepine dimers with DNA binding affinity and  
 cytotoxicity)  
 RN 763125-64-0 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-7-  
 methoxy-8-[3-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-  
 c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (CA INDEX NAME)

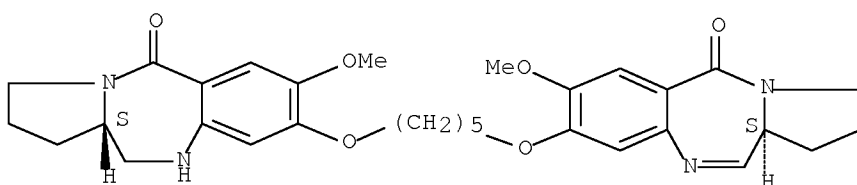
Absolute stereochemistry.



RN 763125-66-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-7-methoxy-8-[[5-[[1,2,3,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



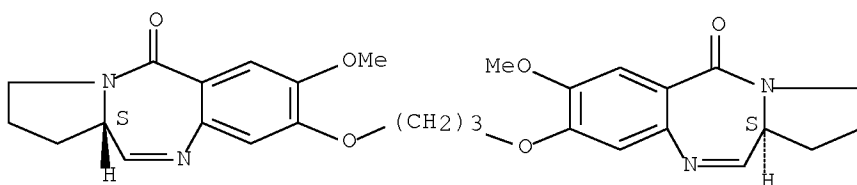
IT 140676-21-7 343308-45-2

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(pyrrolbenzodiazepine dimers with DNA binding affinity and cytotoxicity)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

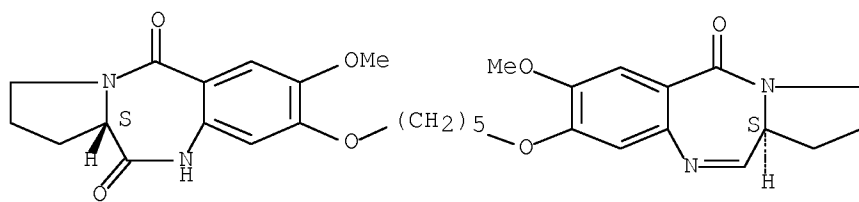
Absolute stereochemistry. Rotation (+).



RN 343308-45-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[[5-[[1,2,3,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 46 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2004:757716 CAPLUS Full-text

DN 141:271175

TI The Novel Sequence-Specific DNA Cross-Linking Agent SJG-136 (NSC 694501) Has Potent and Selective In vitro Cytotoxicity in Human B-Cell Chronic Lymphocytic Leukemia Cells with Evidence of a p53-Independent Mechanism of Cell Kill

AU Pepper, Christopher J.; Hambly, Rachel M.; Fegan, Christopher D.; Delavault, Patrick; Thurston, David E.

CS Department of Haematology, University of Wales College of Medicine, Cardiff, CF14 4XN, UK

SO Cancer Research (2004), 64(18), 6750-6755  
CODEN: CNREA8; ISSN: 0008-5472

PB American Association for Cancer Research

DT Journal

LA English

AB SJG-136 (NSC 694501) is a novel DNA crosslinking agent that binds in a sequence-selective manner in the minor groove of the DNA helix. It is structurally novel compared with other clin. used DNA crosslinking agents and has exhibited a unique multilog differential pattern of activity in the NCI 60-cell line screen (i.e., is COMPARE neg. to other crosslinking agents). Given this profile, the authors undertook a preclin. evaluation of SJG-136 in primary tumor cells derived from 34 B-cell chronic lymphocytic leukemia (B-CLL) patients. SJG-136 induced apoptosis in all of the B-CLL samples tested with a mean LD50 value (the concentration of drug required to kill 50% of the cells) of 9.06 nmol/L. Its cytotoxicity was undiminished in B-CLL cells derived from patients treated previously, those with unmutated VH genes, and those with p53 mutations (P = 0.17; P = 0.63; P = 0.42, resp.). SJG-136-induced apoptosis was associated with the activation of caspase-3 that could be partially abrogated by the caspase-9 inhibitor Z-LEHD-FMK. Furthermore, SJG-136 did not trigger the phosphorylation of p53 or the up-regulation of GADD45 expression in B-CLL cells whereas the crosslinking agent chlorambucil elicited both of these effects. This suggests that SJG-136 crosslinking adducts are not subject to p53-mediated DNA excision repair mechanisms in B-CLL cells. Taken together, these data demonstrate a novel mechanism of action for SJG-136 that appears to circumvent the effects of poor prognostic markers. This unique cytotoxicity profile warrants further investigation and supports the evaluation of this agent in Phase I clin. trials for patients with B-CLL.

IT 232931-57-6, SJG 136

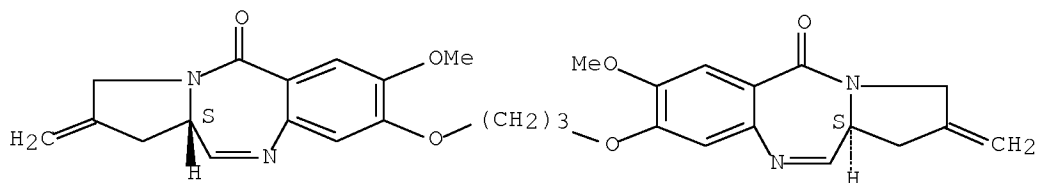
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(NSC 694501; novel sequence-specific DNA crosslinking agent SJG-136 (NSC 694501) has potent and selective in vitro cytotoxicity in human B-cell chronic lymphocytic leukemia cells with evidence of a p53-independent mechanism of cell kill)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

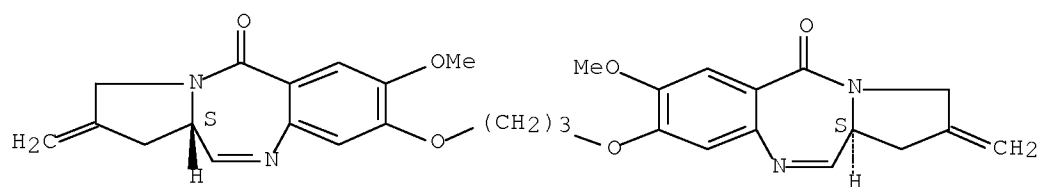
Absolute stereochemistry. Rotation (+).



RE.CNT 20      THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 47 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2004:757703 CAPLUS Full-text  
 DN 141:271174  
 TI SJG-136 (NSC 694501), A Novel Rationally Designed DNA Minor Groove Interstrand Cross-Linking Agent with Potent and Broad Spectrum Antitumor Activity: Part 2: Efficacy Evaluations  
 AU Alley, Michael C.; Hollingshead, Melinda G.; Pacula-Cox, Christine M.; Waud, William R.; Hartley, John A.; Howard, Philip W.; Gregson, Stephen J.; Thurston, David E.; Sausville, Edward A.  
 CS Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda and Frederick, MD, 21701-8527, USA  
 SO Cancer Research (2004), 64(18), 6700-6706  
 CODEN: CNREA8; ISSN: 0008-5472  
 PB American Association for Cancer Research  
 DT Journal  
 LA English  
 AB Pyrrolo[2,1-c][1,4]benzodiazepine dimer SJG-136 (NSC 694501) selectively crosslinks guanine residues located on opposite strands of DNA, and exhibits potent in vitro cytotoxicity. In addition, SJG-136 is highly active in vivo in hollow fiber assays. In the current investigation, SJG-136 was evaluated for in vivo efficacy in 10 tumor models selected on the basis of sensitivity of cells grown in the hollow fiber and in vitro time course assays: LOX IMVI and UACC-62 (melanomas); OVCAR-3 and OVCAR-5 (ovarian carcinomas); MDA-MB-435 (breast carcinoma); SF-295 and C-6 (gliomas); LS-174T (colon carcinoma); HL-60 TB (promyelocytic leukemia); and NCI-H522 (lung carcinoma). SJG-136 was active against small (150 mg) and large (250-400 mg) xenografts with tumor mass redns. in all 10 models. In addition, significant growth delays occurred in nine models, cell kill in six models ranged between 1.9 and 7.2 logs, and there were 1 to 4/6 tumor-free responses in six models. SJG-136 is active following i.v. bolus injections, as well as by 5-day continuous infusions. Of all of the schedules tested, bolus administrations for 5 consecutive days (qdx5) conferred the greatest efficacy. SJG-136 is active over a wide dosage range in athymic mouse xenografts: on a qdx5 schedule, the maximum-tolerated dose was .apprx.120 µg/kg/dose (total dose: 0.6 mg/kg = 1.8 mg/m2) and the min. ED in the most sensitive model (SF-295) was .apprx.16 µg/kg/dose (total dose: 0.08 mg/kg = 0.24 mg/m2). Results of this study extend the initial in vivo observations reported in the reference above and confirm the importance of expediting more detailed preclin. evaluations on this novel agent in support of phase I clin. trials in the United Kingdom and the United States, which are planned to commence shortly.  
 IT 232931-57-6, SJG 136  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (efficacy of SJG-136 (NSC 694501), a novel rationally designed DNA minor groove interstrand crosslinking agent with potent and broad spectrum antitumor activity)  
 RN 232931-57-6 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

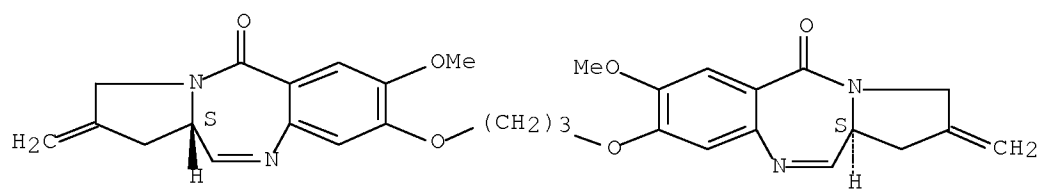


RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



L18 ANSWER 48 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2004:757702 CAPLUS Full-text  
 DN 141:271173  
 TI SJG-136 (NSC 694501), a Novel Rationally Designed DNA Minor Groove Interstrand Cross-Linking Agent with Potent and Broad Spectrum Antitumor Activity: Part 1: Cellular Pharmacology, In vitro and Initial In vivo Antitumor Activity  
 AU Hartley, John A.; Spanswick, Victoria J.; Brooks, Natalie; Clingen, Peter H.; McHugh, Peter J.; Hochhauser, Daniel; Pedley, R. Barbara; Kelland, Lloyd R.; Alley, Michael C.; Schultz, Robert; Hollingshead, Melinda G.; Schweikart, Karen M.; Tomaszewski, Joseph E.; Sausville, Edward A.; Gregson, Stephen J.; Howard, Philip W.; Thurston, David E.  
 CS Cancer Research UK Drug-DNA Interactions Research Group and Cancer Research UK Targeting and Imaging Research Group, Department of Oncology, Royal Free and University College Medical School, London, W1W 7BS, UK  
 SO Cancer Research (2004), 64(18), 6693-6699  
 CODEN: CNREA8; ISSN: 0008-5472  
 PB American Association for Cancer Research  
 DT Journal  
 LA English  
 AB SJG-136 (NSC 694501) is a rationally designed pyrrolobenzodiazepine dimer that binds in the minor groove of DNA. It spans 6 bp with a preference for binding to purine-GATC-pyrimidine sequences. The agent has potent activity in the National Cancer Institute (NCI) anticancer drug screen with 50% net growth inhibition conferred by 0.14 to 320 nmol/L (7.4 nmol/L mean). Sensitive cell lines exhibit total growth inhibition and 50% lethality after treatment with as little as 0.83 and 7.1 nmol/L SJG-136, resp. COMPARE and mol. target anal. of SJG-136 data vs. that of >60,000 compds. tested in the NCI 60 cell line screen shows that, although the agent has similarity to other DNA binding agents, the pattern of activity for SJG-136 does not fit within the clusters of any known agents, suggesting that SJG-136 possesses a distinct mechanism of action. Testing in the NCI standard hollow fiber assay produced prominent growth inhibition in 20 of 24 i.p. and 7 of 24 s.c. test combinations with 5 of 12 cell lines exhibiting cell kill. In addition, SJG-136 produced antitumor activity in mice bearing CH1 and CH1cisR xenografts, a cisplatin-resistant human ovarian tumor model, and also in mice bearing LS174T xenografts, a human colon tumor model. SJG-136 produces DNA interstrand crosslinks between two N-2 guanine positions on opposite strands and separated by 2 bp. In human tumor cell lines, the crosslinks form rapidly and persist compared with those produced by conventional crosslinking agents such as nitrogen mustards. In mice bearing the LS174T human colon xenograft, DNA interstrand crosslinks can be detected in tumor cells using a modification of the single cell gel electrophoresis (comet) assay after administration of a therapeutic dose. Crosslinks in the tumor increase with dose and are clearly detectable at 1 h after i.v. administration. The level of crosslinking persists over a 24-h period in this tumor in contrast to crosslinks produced by conventional crosslinking agents observed over the same time period.  
 IT 232931-57-6, SJG 136  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (SJG-136 (NSC 694501), a rationally designed DNA minor groove interstrand crosslinking agent with potent and broad spectrum antitumor activity)  
 RN 232931-57-6 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

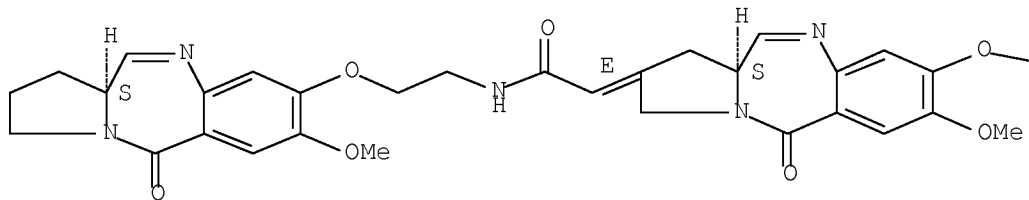


RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 49 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2004:580808 CAPLUS Full-text  
 DN 141:277599  
 TI Synthesis and DNA binding affinity of novel A-C8/C-C2-exo unsaturated  
 alkoxyamido-linked pyrrolo[2,1-c][1,4]benzodiazepine dimers  
 AU Kamal, Ahmed; Srinivas, O.; Ramulu, P.; Ramesh, G.; Kumar, P. Praveen;  
 Kumar, M. Shiva  
 CS Biotransformation Laboratory, Division of Organic Chemistry, Indian  
 Institute of Chemical Technology, Hyderabad, 500007, India  
 SO Bioorganic & Medicinal Chemistry (2004), 12(16), 4337-4350  
 CODEN: BMECEP; ISSN: 0968-0896  
 PB Elsevier Ltd.  
 DT Journal  
 LA English  
 OS CASREACT 141:277599  
 AB The synthesis of novel A-C8/C-C2-exo unsatd. alkoxyamido-linked pyrrolo[2,1-  
 c][1,4]benzodiazepine dimers is reported and these dimers show significant DNA  
 binding affinity and they also exhibit moderate anticancer activity.  
 IT 757190-03-7P 757190-04-8P 757190-05-9P  
 757190-06-0P 757190-13-9P 757190-14-0P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL  
 (Biological study); PREP (Preparation)  
 (stereoselective preparation, DNA binding affinity and antitumor activity  
 of unsatd. alkoxyamido-linked pyrrolobenzodiazepine dimers utilizing  
 chiral starting materials)  
 RN 757190-03-7 CAPLUS  
 CN Acetamide, 2-[(11aS)-5,11a-dihydro-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-  
 pyrrolo[2,1-c][1,4]benzodiazepin-2(3H)-ylidene]-N-[2-[[ (11aS)-2,3,5,11a-  
 tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-  
 yl]oxy]ethyl]-, (2E)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
 Double bond geometry as described by E or Z.

PAGE 1-A



PAGE 1-B

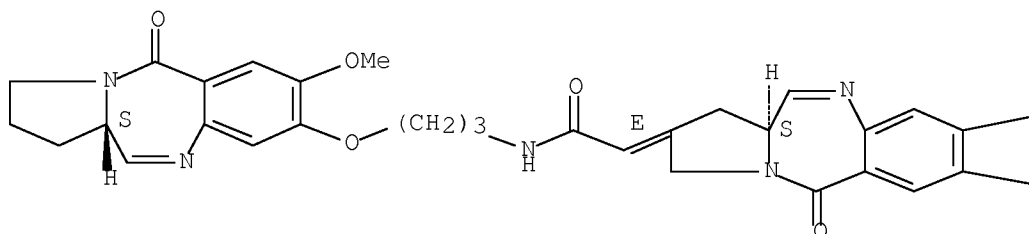


RN 757190-04-8 CAPLUS  
 CN Acetamide, 2-[(11aS)-5,11a-dihydro-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-  
 pyrrolo[2,1-c][1,4]benzodiazepin-2(3H)-ylidene]-N-[3-[[ (11aS)-2,3,5,11a-  
 tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-

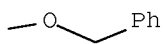
yl]oxy]propyl]-, (2E)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as described by E or Z.

PAGE 1-A



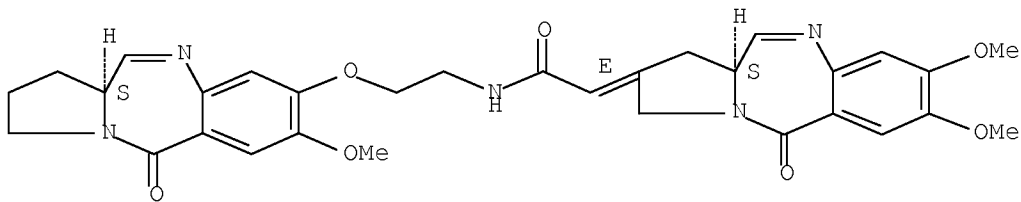
PAGE 1-B



RN 757190-05-9 CAPLUS

CN Acetamide, 2-[(11aS)-5,11a-dihydro-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2(3H)-ylidene]-N-[2-[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]ethyl]-, (2E)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as described by E or Z.

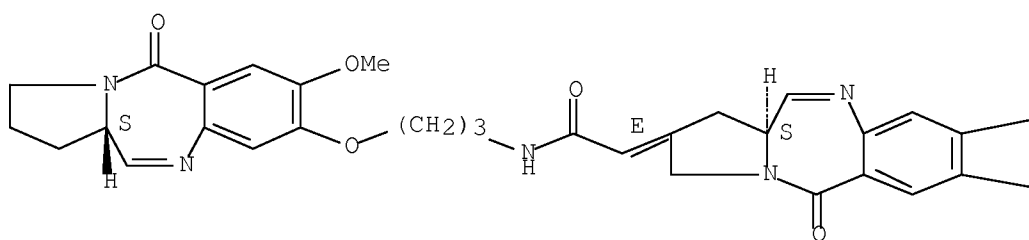


RN 757190-06-0 CAPLUS

CN Acetamide, 2-[(11aS)-5,11a-dihydro-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2(3H)-ylidene]-N-[3-[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propyl]-, (2E)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as described by E or Z.

PAGE 1-A



PAGE 1-B

— OMe

— OMe

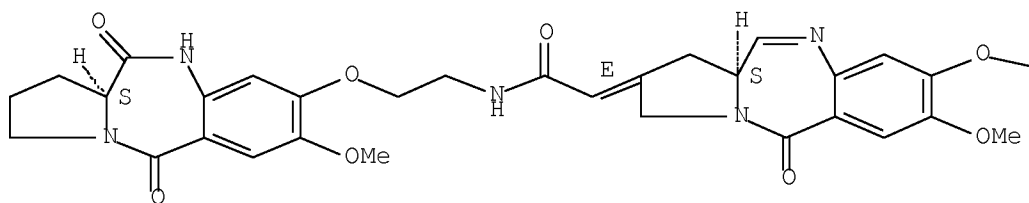
RN 757190-13-9 CAPLUS

CN Acetamide, 2-[(11aS)-5,11a-dihydro-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2(3H)-ylidene]-N-[2-[[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]ethyl]-, (2E)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

— Ph

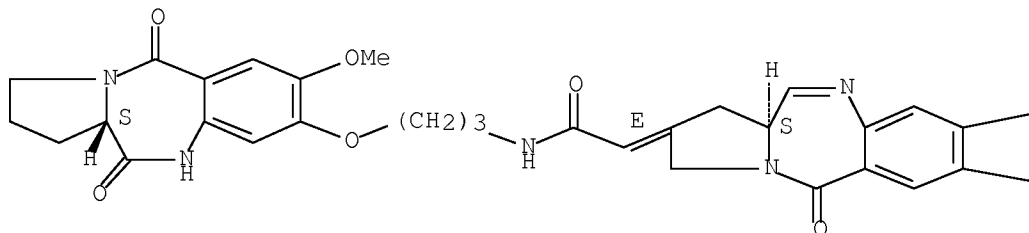
RN 757190-14-0 CAPLUS

CN Acetamide, 2-[(11aS)-5,11a-dihydro-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2(3H)-ylidene]-N-[3-[[[(11aS)-

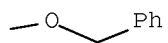
2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propyl]-, (2E)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as described by E or Z.

PAGE 1-A



PAGE 1-B



RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 50 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2004:359111 CAPLUS Full-text

DN 142:173

TI Preliminary pharmacokinetic and bioanalytical studies of SJG-136 (NSC 694501), a sequence-selective pyrrolobenzodiazepine dimer DNA-cross-linking agent

AU Wilkinson, Gary P.; Taylor, James P.; Shnyder, Steve; Cooper, Patricia; Howard, Phil W.; Thurston, David E.; Jenkins, Terence C.; Loadman, Paul M.

CS Tom Connors Cancer Research Centre, Cancer Research UK Cancer Research Unit, University of Bradford, West Yorkshire, BD7 3AY, UK

SO Investigational New Drugs (2004), 22(3), 231-240

CODEN: INNDDK; ISSN: 0167-6997

PB Kluwer Academic Publishers

DT Journal

LA English

AB SJG-136 is a synthetic pyrrolobenzodiazepine (PBD) dimer in which two DNA-alkylating subunits are linked through an inert propanedioxy tether. Biophys. and biochem. studies of SJG-136 have shown a remarkable affinity for DNA and potent cytotoxicity in vitro. On this basis, together with its unique sequence selectivity and interstrand DNA crosslinking activity, SJG-136 has been selected for clin. trials. This study examines the pharmacol. characteristics of SJG-136 and provides the first report of pharmacokinetic properties for this agent. A sensitive, selective and reproducible reversed-phase gradient LC/MS assay has been developed for detection and anal., where a mol. ion (m/z 557.2) is detectable for the SJG-136 parent imine. Fluorescence detection (260 nm excitation, 420 nm emission) gives a limit of sensitivity of 5 nM (2.5 ng ml<sup>-1</sup>) for anal. of SJG-136 in mouse plasma. Extraction efficiencies from plasma were >65% across a range of concns. (5-1000 nM). Following administration to mice at the MTD (i.p., 0.2 mg kg<sup>-1</sup>), high peak plasma concns. of SJG-136 were seen (C<sub>max</sub> = 336 nM) at 30 min after dosing. A calculated terminal t<sub>1/2</sub> of 0.98 h and AUC of 0.34 µM·h resulted in a clearance rate of 17.7 mL min<sup>-1</sup> kg<sup>-1</sup>. The PBD dimer binds only moderately to proteins (65-75%), and in vitro cytotoxicity studies confirmed IC<sub>50</sub> values of 4-30 nM with a panel of human cell lines. This finding demonstrates that plasma concns. achieved in the mouse are substantially higher than those required to elicit an anti tumor response in vitro. This report forms an important phase in the pre-clin. characterization of the compound

IT 232931-57-6, SJG-136

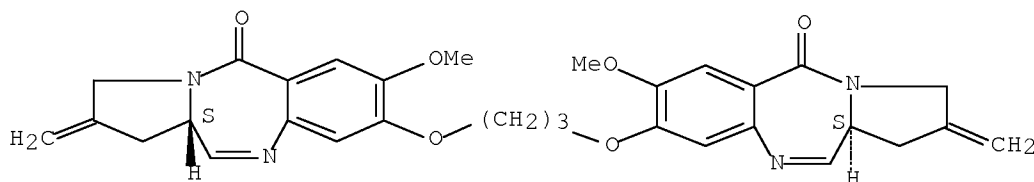
RL: PKT (Pharmacokinetics); BIOL (Biological study)

(pharmacokinetic study revealed that peak plasma concentration of SJC-136 achieved in mouse are substantially higher than those required to elicit anti-tumor response in vitro)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

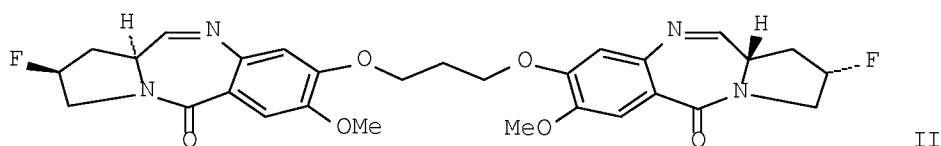
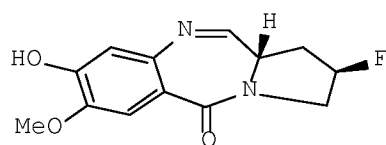
Absolute stereochemistry. Rotation (+).



RE.CNT 19      THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

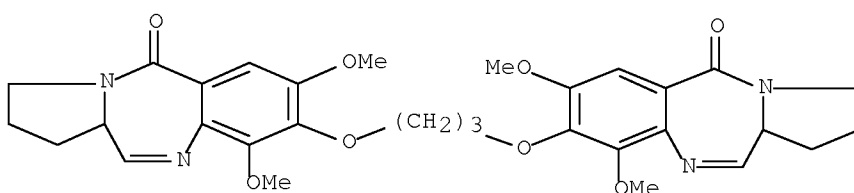


L18 ANSWER 51 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2004:346285 CAPLUS Full-text  
 DN 141:106440  
 TI The effect of C2-fluoro group on the biological activity of DC-81 and its dimers  
 AU Kamal, Ahmed; Reddy, P. S. M. M.; Reddy, D. Rajasekhar  
 CS Division of Organic Chemistry, Biotransformation Laboratory, Indian Institute of Chemical Technology, Hyderabad, 500007, India  
 SO Bioorganic & Medicinal Chemistry Letters (2004), 14(10), 2669-2672  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Science B.V.  
 DT Journal  
 LA English  
 OS CASREACT 141:106440  
 GI



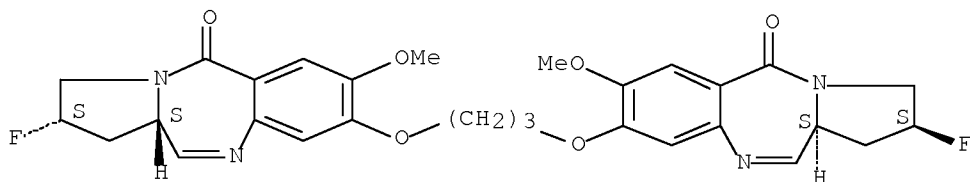
AB C2-Fluoro substituted pyrrolobenzodiazepines were synthesized that exhibit potential anticancer activity in a number of human tumor cell lines. These C2-fluoro substituted PBDs also exhibit significant DNA-binding ability. Example compds. included (2R,11aS)-2-Fluoro-1,2,3,11a-tetrahydro-8-hydroxy- 7-methoxy-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (I) and a dimer (II).  
 IT 260546-09-6, (11aS,11'aS)-8,8'-[1,3-Propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7,9-dimethoxy-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one  
 RL: PAC (Pharmacological activity); BIOL (Biological study)  
 (preparation of (fluoro)tetrahydro(hydroxy)pyrrolo[2,1-c][1,4]benzodiazepin-5-one derivs. and dimers and study of their anticancer activity)  
 RN 260546-09-6 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7,9-dimethoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



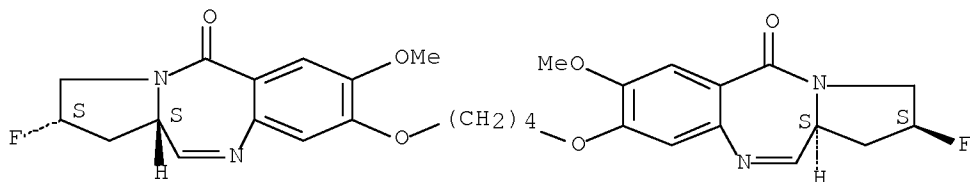
IT 717920-82-6P 717920-83-7P 717920-84-8P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL  
 (Biological study); PREP (Preparation)  
 (preparation of (fluoro)tetrahydro(hydroxy)pyrrolo[2,1-  
 c][1,4]benzodiazepin-  
 5-one derivs. and dimers and study of their anticancer activity)  
 RN 717920-82-6 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
 propanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-,  
 (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



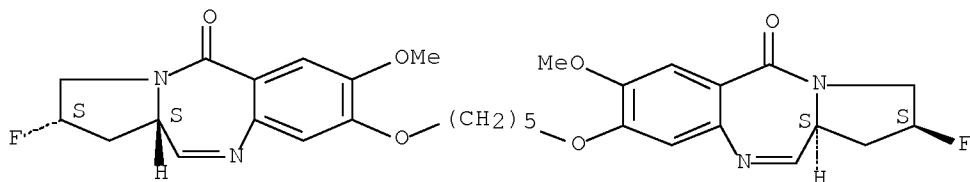
RN 717920-83-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-  
 butanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-,  
 (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 717920-84-8 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-  
 pentanediylbis(oxy)]bis[2-fluoro-1,2,3,11a-tetrahydro-7-methoxy-,  
 (2S,2'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 24      THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 52 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2004:79123 CAPLUS Full-text

DN 140:280775

TI Linker Length Modulates DNA Cross-Linking Reactivity and Cytotoxic Potency of C8/C8' Ether-Linked C2-exo-Unsaturated Pyrrolo[2,1-c][1,4]benzodiazepine (PBD) Dimers

AU Gregson, Stephen J.; Howard, Philip W.; Gullick, Darren R.; Hamaguchi, Anzu; Corcoran, Kathryn E.; Brooks, Natalie A.; Hartley, John A.; Jenkins, Terence C.; Patel, Sejal; Guille, Matthew J.; Thurston, David E.

CS Cancer Research UK Gene Targeted Drug Design Research Group, The School of Pharmacy, University of London, London, WC1N 1AX, UK

SO Journal of Medicinal Chemistry (2004), 47(5), 1161-1174  
CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

OS CASREACT 140:280775

AB A C2/C2'-exo-unsatd. pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimer (DRG-16) with a C8-O(CH<sub>2</sub>)<sub>n</sub>O-C8' diether linkage (n = 5) has been synthesized that shows markedly superior in vitro cytotoxic potency (e.g., >3400-fold in IGROV1 ovarian cells) and interstrand DNA crosslinking reactivity (>10-fold) compared to the shorter homolog (SJG-136; n = 3). In contrast, for the C-ring unsubstituted series, the corresponding n = 5 dimer is generally less cytotoxic and has a lower interstrand crosslinking reactivity compared to its shorter n = 3 homolog. Dimer DRG-16 cross-links DNA with >10-fold efficiency compared to 4a, and also inhibits the activity of the restriction endonuclease BamH1 more efficiently. The C2-exo-unsatd. PBD dimers 4a,b are not only more effective than their C-ring saturated counterparts in terms of induced ΔT<sub>m</sub> shift, but they also exert this effect more rapidly. Mol. modeling shows a rank order of DRG-16 (n = 5) > SJG-136 (n = 3) in terms of binding energy toward duplexes containing embedded target 5'-GAT1-2C cross-link sequences, reflecting the superior fit of the C2-exo-unsatd. rather than saturated C-rings of the PBD dimers. A novel synthesis of core synthetic building blocks for PBD dimers via stepwise Mitsunobu reaction and nitration with Cu(NO<sub>3</sub>)<sub>2</sub> is also reported.

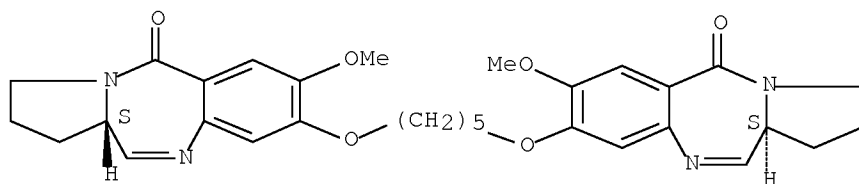
IT 145325-57-1 145325-58-2

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(linker length modulates DNA crosslinking reactivity and cytotoxic potency of C8/C8' ether-linked C2-exo-unsatd. pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimers)

RN 145325-57-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediy]bis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

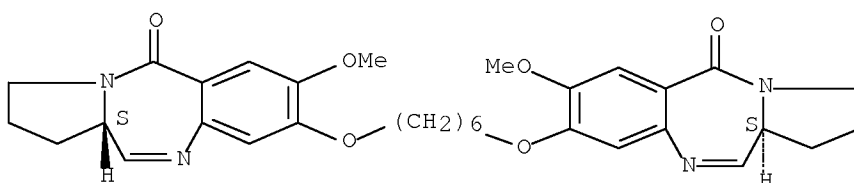


RN 145325-58-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,6-

hexanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

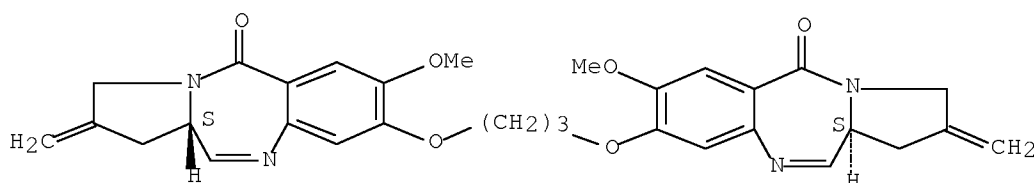


IT 232931-57-6P, SJG 136 260417-62-7P  
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(linker length modulates DNA crosslinking reactivity and cytotoxic potency of C8/C8' ether-linked C2-exo-unsatd. pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimers)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

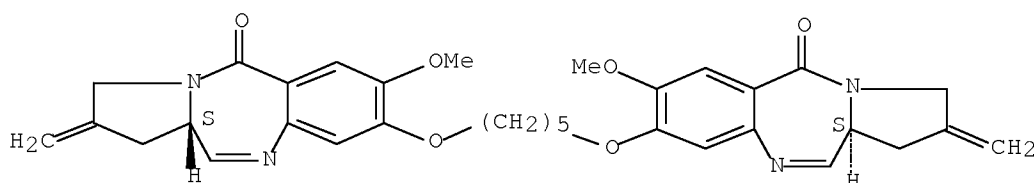
Absolute stereochemistry. Rotation (+).



RN 260417-62-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediybis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 140676-21-7 145325-56-0

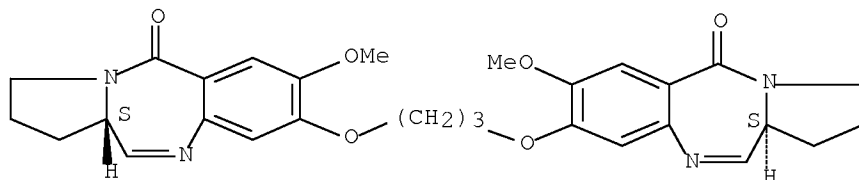
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(linker length modulates DNA crosslinking reactivity and cytotoxic potency of C8/C8' ether-linked C2-exo-unsatd. pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimers)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

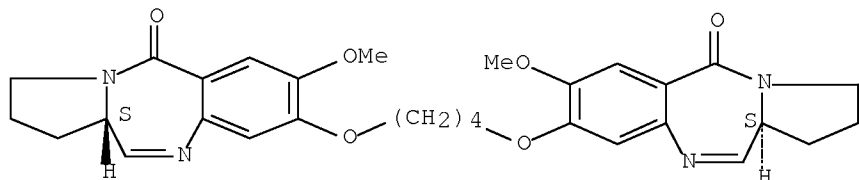
Absolute stereochemistry. Rotation (+).



RN 145325-56-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

Absolute stereochemistry.



IT 232931-64-SF 260418-31-3F

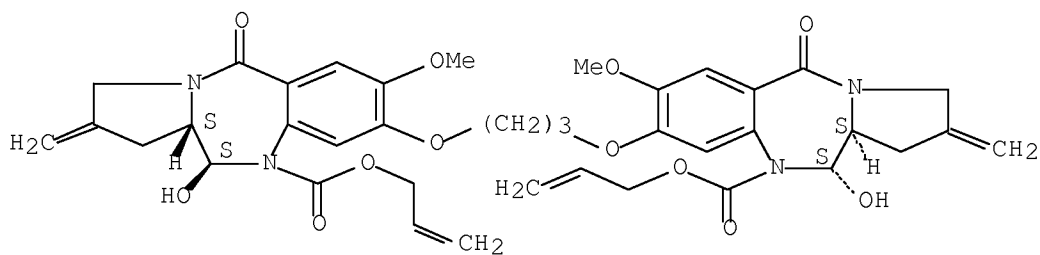
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(linker length modulates DNA crosslinking reactivity and cytotoxic potency of C8/C8' ether-linked C2-exo-unsatd. pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimers)

RN 232931-64-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

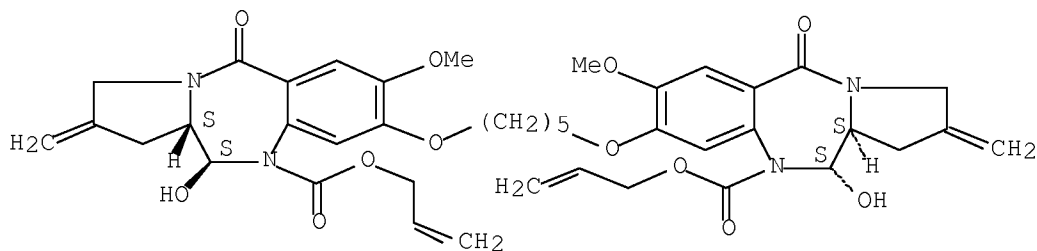
Absolute stereochemistry.



RN 260418-31-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,5-pentanediy]bis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-  
(9CI) (CA INDEX NAME)

Absolute stereochemistry.

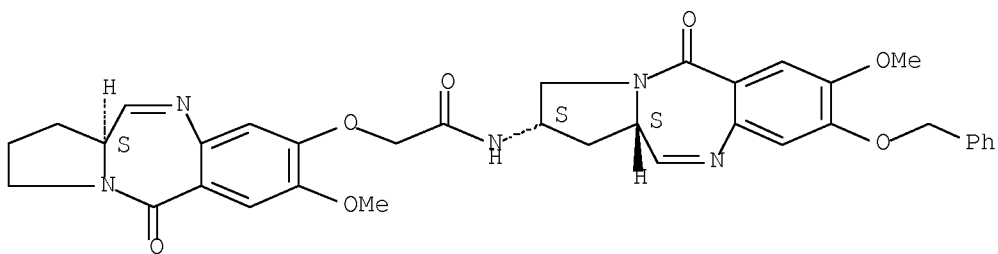


RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 53 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2003:841816 CAPLUS Full-text  
 DN 140:94019  
 TI Synthesis and DNA-binding affinity of A-C8/C-C2 alkoxyamido-linked  
 pyrrolo[2,1-c][1,4]benzodiazepine dimers  
 AU Kamal, Ahmed; Ramulu, P.; Srinivas, O.; Ramesh, G.  
 CS Division of Organic Chemistry, Indian Institute of Chemical Technology,  
 Hyderabad, 500007, India  
 SO Bioorganic & Medicinal Chemistry Letters (2003), 13(22), 3955-3958  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Science B.V.  
 DT Journal  
 LA English  
 OS CASREACT 140:94019  
 AB The synthesis of new A-C8/C-C2 alkoxyamido-linked pyrrolo[2,1-  
 c][1,4]benzodiazepine dimers have been described in this report. These dimers  
 exhibit significant DNA-binding ability with moderate anticancer activity.  
 Compds. thus prepared included [[(11aS)-2,3,5,11a-tetrahydro-7- methoxy-5-oxo-  
 1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)-2,3,5,11a-  
 tetrahydro-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-  
 c][1,4]benzodiazepin-2-yl]acetamide, 4-[[[(11aS)-2,3,5,11a-tetrahydro-7-  
 methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)-  
 2,3,5,11a-tetrahydro-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-  
 c][1,4]benzodiazepin-2-yl]butanamide, 5-[[[(11aS)-2,3,5,11a-tetrahydro-7-  
 methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)-  
 2,3,5,11a-tetrahydro-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-  
 c][1,4]benzodiazepin-2-yl]pentanamide. Corresponding dioxo compds., i.e.,  
 [[(11aS)-2,3,5,11a-Tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-  
 c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)-2,3,5,10,11,11a-hexahydro-7-  
 methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]acetamide and  
 homologs, were also prepared and tested.  
 IT 642478-96-4P, [[(11aS)-2,3,5,11a-Tetrahydro-7-methoxy-5-oxo-1H-  
 pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)-2,3,5,11a-  
 tetrahydro-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-  
 c][1,4]benzodiazepin-2-yl]acetamide 642478-97-5P,  
 4-[[[(11aS)-2,3,5,11a-Tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-  
 c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)-2,3,5,11a-tetrahydro-7-methoxy-  
 5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-  
 yl]butanamide 642478-98-6P 642479-12-7P,  
 [[(11aS)-2,3,5,11a-Tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-  
 c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)-2,3,5,10,11,11a-hexahydro-7-  
 methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]acetamide  
 642479-14-9P, 4-[[[(11aS)-2,3,5,11a-Tetrahydro-7-methoxy-5-oxo-1H-  
 pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)-2,3,5,10,11,11a-  
 hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-  
 yl]butanamide 642479-15-0P, 5-[[[(11aS)-2,3,5,11a-Tetrahydro-7-  
 methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)-  
 2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-  
 c][1,4]benzodiazepin-2-yl]pentanamide  
 RL: BSU (Biological study, unclassified); PAC (Pharmacological activity);  
 SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (preparation and DNA-binding affinity of alkoxyamido-linked  
 pyrrolo[2,1-c][1,4]benzodiazepine dimers)  
 RN 642478-96-4 CAPLUS  
 CN Acetamide, N-[(2S,11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-8-  
 (phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]-2-[[[(11aS)-  
 2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-  
 yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry.



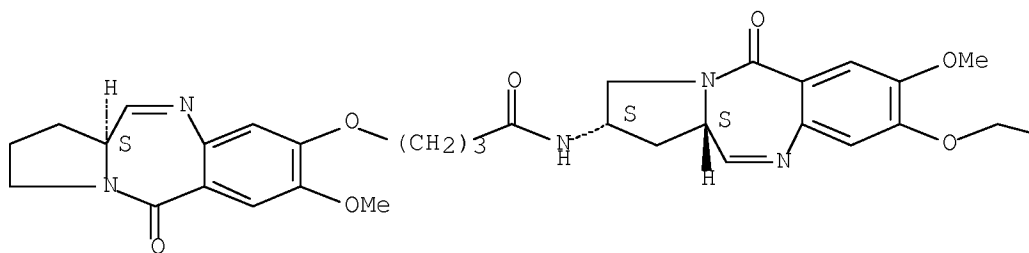


RN 642478-97-5 CAPLUS

CN Butanamide, N-[(2S,11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]-4-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



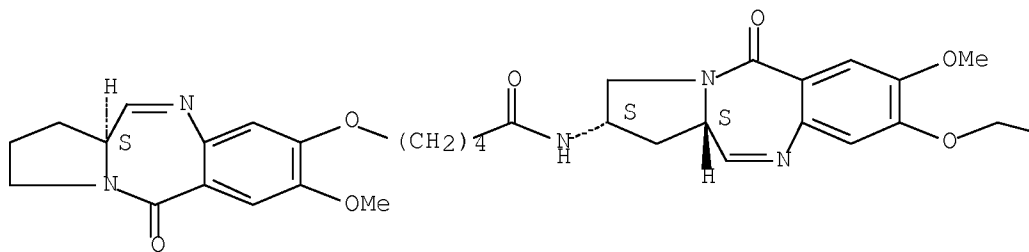
PAGE 1-B

— Ph

RN 642478-98-6 CAPLUS

CN Pentanamide, N-[(2S,11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]-5-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry.

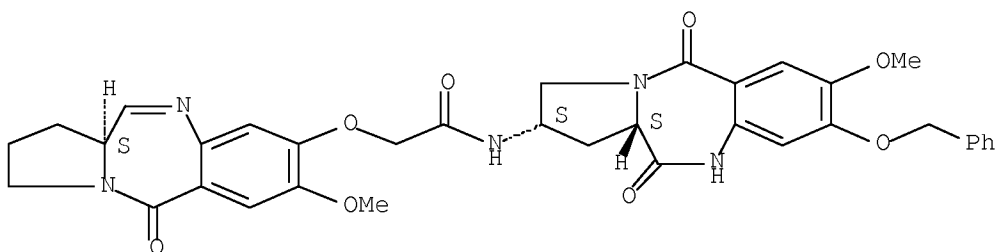


— Ph

RN 642479-12-7 CAPLUS

CN Acetamide, N-[(2S,11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]-2-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry.

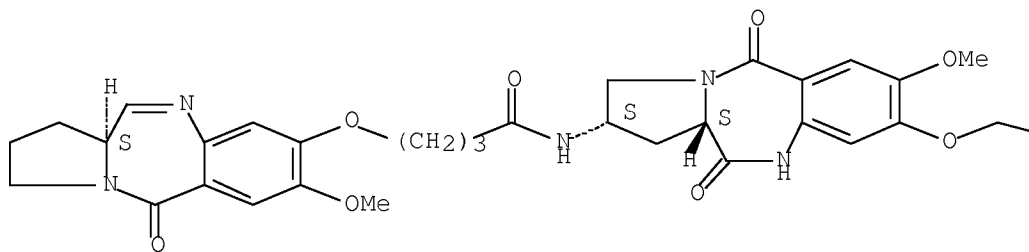


RN 642479-14-9 CAPLUS

CN Butanamide, N-[(2S,11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]-4-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



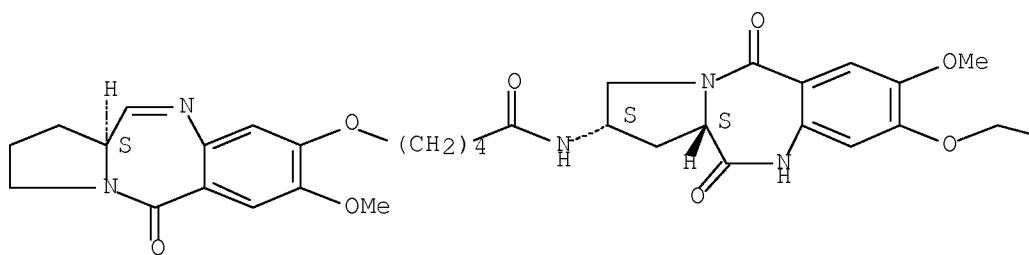
PAGE 1-B

— Ph

RN 642479-15-0 CAPLUS  
 CN Pentanamide, N-[(2S,11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]-5-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



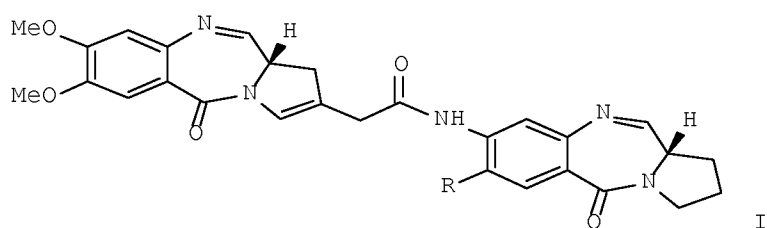
PAGE 1-B

— Ph

RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

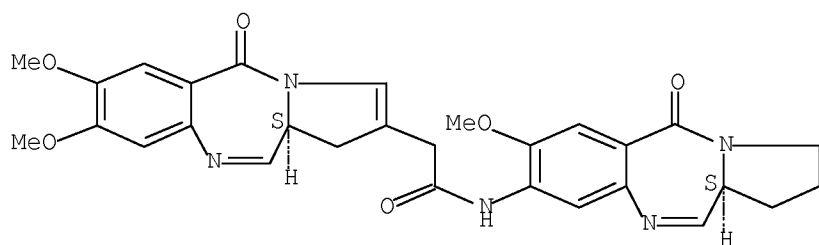


L18 ANSWER 54 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2003:485873 CAPLUS Full-text  
 DN 139:261068  
 TI Synthesis of the first examples of A-C8/C-C2 amide-Linked  
 pyrrolo[2,1-c][1,4]benzodiazepine dimers  
 AU Gregson, Stephen J.; Howard, Philip W.; Thurston, David E.  
 CS The School of Pharmacy, Cancer Research UK Gene Targeted Drug Design  
 Research Group, University of London, London, WC1N 1AX, UK  
 SO Bioorganic & Medicinal Chemistry Letters (2003), 13(14), 2277-2280  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Science B.V.  
 DT Journal  
 LA English  
 OS CASREACT 139:261068  
 GI



AB The novel A-C8/C-C2 amide-linked pyrrolo[2,1-c][1,4]benzodiazepine dimers I (R = H, MeO) were prepared via a convergent routes. These compds. lack the potent DNA interstrand crosslinking ability and resultant pronounced cytotoxicity of the known A-C8/A-C8' linked dimers.  
 IT 600713-72-2P 600713-73-3P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (synthesis of first examples of A-C8/C-C2 amide-Linked pyrrolo[2,1-c][1,4]benzodiazepine dimers)  
 RN 600713-72-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acetamide, 5,11a-dihydro-7,8-dimethoxy-5-oxo-N-[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]-, (11aS)- (CA INDEX NAME)

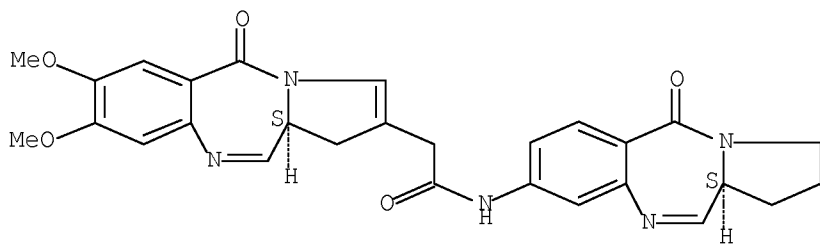
Absolute stereochemistry.



RN 600713-73-3 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acetamide, 5,11a-dihydro-7,8-

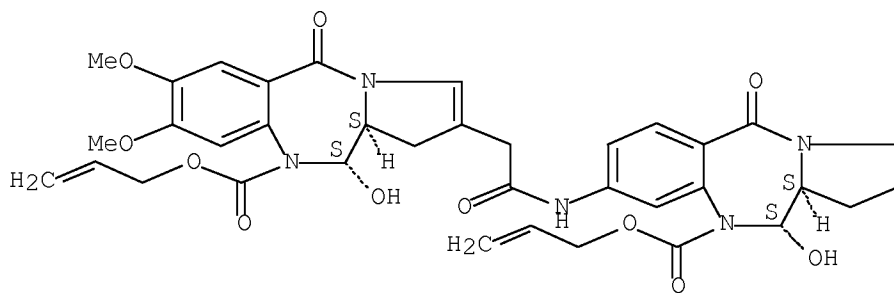
dimethoxy-5-oxo-N-[(11aS)-2,3,5,11a-tetrahydro-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry.



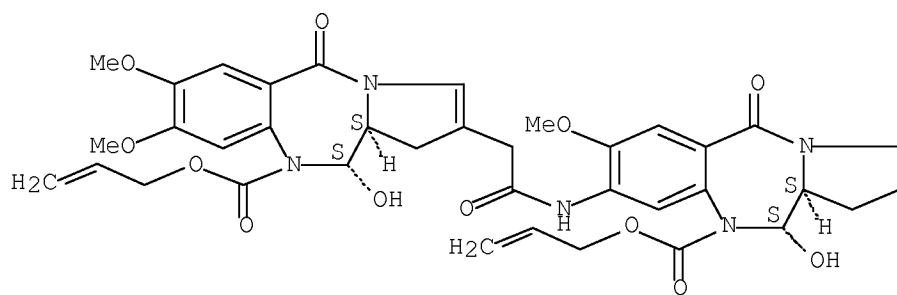
IT 600713-87-9P 600713-88-0P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (synthesis of first examples of A-C8/C-C2 amide-Linked pyrrolo[2,1-c][1,4]benzodiazepine dimers)  
 RN 600713-87-9 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2-[2-[[[(11S,11aS)-2,3,5,10,11,11a-hexahydro-11-hydroxy-5-oxo-10-[(2-propen-1-yloxy)carbonyl]-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]amino]-2-oxoethyl]-11,11a-dihydro-11-hydroxy-7,8-dimethoxy-5-oxo-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



RN 600713-88-0 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2-[2-[[[(11S,11aS)-2,3,5,10,11,11a-hexahydro-11-hydroxy-7-methoxy-5-oxo-10-[(2-propen-1-yloxy)carbonyl]-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]amino]-2-oxoethyl]-11,11a-dihydro-11-hydroxy-7,8-dimethoxy-5-oxo-, 2-propen-1-yl ester, (11S,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 55 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2003:459751 CAPLUS Full-text

DN 139:175324

TI Sequence-Selective Recognition of Duplex DNA through Covalent Interstrand Cross-Linking: Kinetic and Molecular Modeling Studies with Pyrrolobenzodiazepine Dimers

AU Smellie, Melissa; Bose, Deravander S.; Thompson, Andrew S.; Jenkins, Terence C.; Hartley, John A.; Thurston, David E.

CS Cancer Research UK Drug-DNA Interactions Research Group, Department of Oncology, Royal Free University, College Medical School, UCL, London, W1W 7BS, UK

SO Biochemistry (2003), 42(27), 8232-8239

CODEN: BICHAW; ISSN: 0006-2960

PB American Chemical Society

DT Journal

LA English

AB Members of a homologous series of pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimers with C8-O-(CH<sub>2</sub>)<sub>n</sub>-O-C8' diether linkages (n = 3-6) have been studied for their ability to interact with oligonucleotide duplexes containing potential target binding sites. The results confirm earlier predictions that the n = 3 analog (DSB-120) will covalently bind to a 5'-Pu-GATC-Py sequence by crosslinking opposite-strand guanines separated by 2 bp. Preference for this DNA sequence is shown using oligonucleotides with altered bases between and/or flanking these guanines. The more extended PBD dimer (n = 5) can span an extra base pair and cross-link the 5'-Pu-GA(T/A)TC-Py sequence. The ability of each homolog to cross-link linear plasmid DNA has been determined, with a rank order that correlates with the reported order of in vitro cytotoxicity: n = 3 > n = 5 > n = 6 > n = 4. The n = 3 homolog is >300-fold more efficient at crosslinking DNA than the clin. used crosslinking agent melphalan under the same conditions. Kinetic studies reveal that the n = 3 and 5 dimers achieve faster crosslinking to plasmid DNA (108 and 81% crosslinking h<sup>-1</sup> μM<sup>-1</sup> at 37°, resp.), whereas the n = 4 and 6 homologs are significantly less efficient at 10.3 and 23% crosslinking h<sup>-1</sup> μM<sup>-1</sup>, resp. Alternating activity for the odd n and even n dimers is probably due to configurational factors governed by the spatial separation of the PBD subunits and the flexible character of the tethering linkage. Mol. modeling confirms the order of crosslinking reactivity, and highlights the role of linker length in dictating sequence recognition for this class of DNA-reactive agent.

IT 140676-21-7 145325-56-0 145325-57-1  
145325-58-2

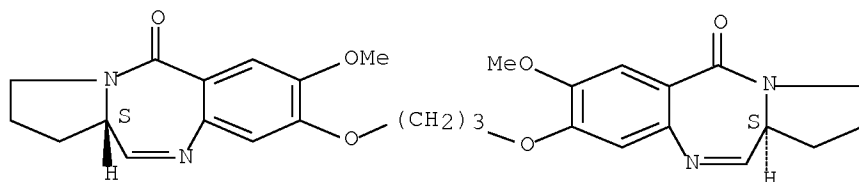
RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)

(DNA covalent interstrand crosslinking with pyrrolobenzodiazepine dimers)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

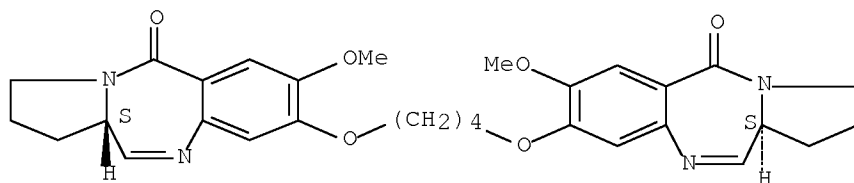
Absolute stereochemistry. Rotation (+).





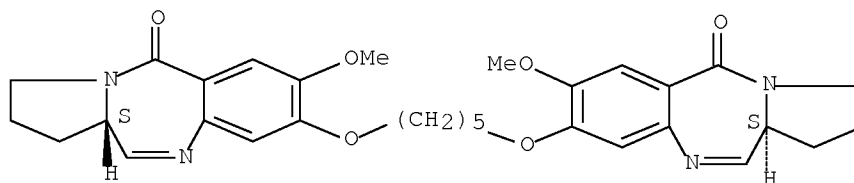
RN 145325-56-0 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.



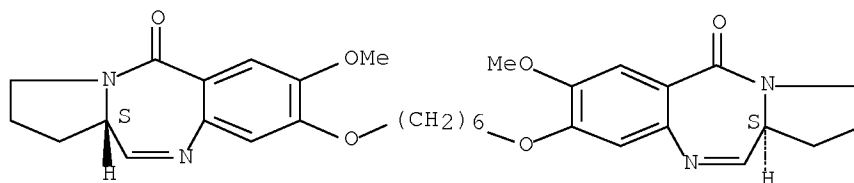
RN 145325-57-1 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediyibis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



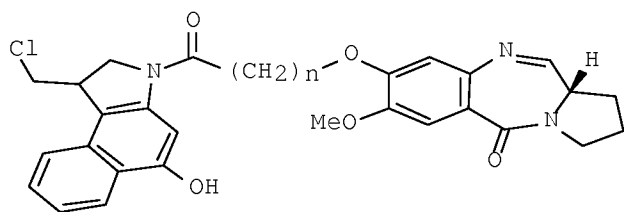
RN 145325-58-2 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,6-hexanediyibis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

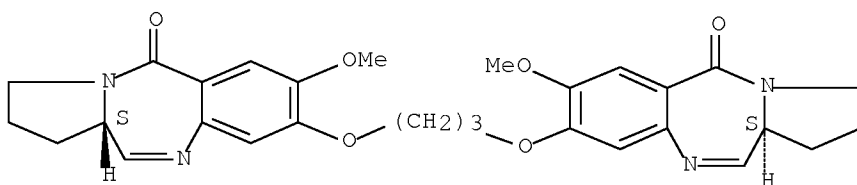
L18 ANSWER 56 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2003:323970 CAPLUS Full-text  
 DN 139:69239  
 TI Unsymmetrical DNA Cross-Linking Agents: Combination of the CBI and PBD Pharmacophores  
 AU Tercel, Moana; Stribbling, Stephen M.; Sheppard, Hilary; Siim, Bronwyn G.; Wu, Kent; Pullen, Susan M.; Botting, K. Jane; Wilson, William R.; Denny, William A.  
 CS Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, University of Auckland, Auckland, 92019, N. Z.  
 SO Journal of Medicinal Chemistry (2003), 46(11), 2132-2151  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 139:69239  
 GI



AB A set of chiral amides I ( $n = 1 - 5$ ), each combining the seco-1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol-4-one (seco-CBI) and pyrrolo[2,1-c][1,4]benzodiazepine (PBD) pharmacophores, was designed and prepared. I were anticipated to cross-link between N3 of adenine and N2 of guanine in the minor groove of DNA. The compds., which differ in the chain length separating the two alkylation subunits, and the configuration of the CBI portion, showed great variation in cellular toxicity (over 4 orders of magnitude in a cell line panel) with the most potent example exhibiting IC<sub>50</sub>s in the pM range. Cytotoxicity correlated with the ability of I to cross-link naked DNA. Crosslinking was also observed in living cells, at much lower concns. than for a related sym. PBD dimer. A thermal cleavage assay was used to assess sequence selectivity, demonstrating that the CBI portion controlled the alkylation sites, while the PBD substituent increased the overall efficiency of alkylation. Several compds. were tested for in vivo activity using a tumor growth delay assay against WiDr human colon carcinoma xenografts, with (S,S)-I ( $n = 5$ ) (the most cytotoxic and most efficient cross-linker) showing a statistically significant increase in survival time following a single iv dose.

IT 140676-21-7P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (preparation of chiral (dihydrobenzindolyl)oxoalkoxy pyrrolodiazepinones as unsym. DNA crosslinking and antitumor agents)  
 RN 140676-21-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 550356-53-1F

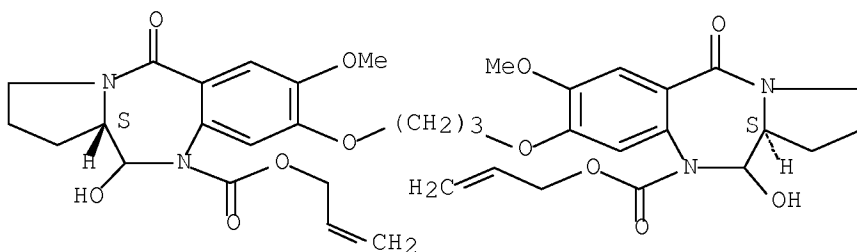
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of chiral (dihydrobenzindolyl)oxoalkoxy pyrrolodiazepinones as unsym. DNA crosslinking and antitumor agents)

RN 550356-53-1 CAPLUS

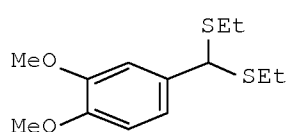
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, di-2-propenyl ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

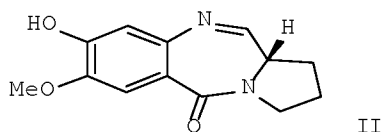


RE.CNT 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 57 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2003:215673 CAPLUS Full-text  
 DN 139:101109  
 TI An efficient catalytic deprotection of thioacetals employing bismuth triflate: synthesis of pyrrolo[2,1-c] [1,4] benzodiazepines  
 AU Kamal, Ahmed; Reddy, P. S. M. M.; Rajasekhar Reddy, D.  
 CS Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad, 500 007, India  
 SO Tetrahedron Letters (2003), 44(14), 2857-2860  
 CODEN: TELEAY; ISSN: 0040-4039  
 PB Elsevier Science Ltd.  
 DT Journal  
 LA English  
 OS CASREACT 139:101109  
 GI



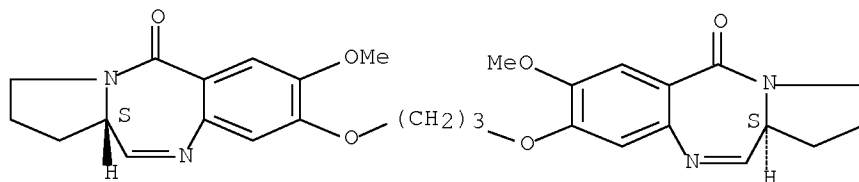
I



II

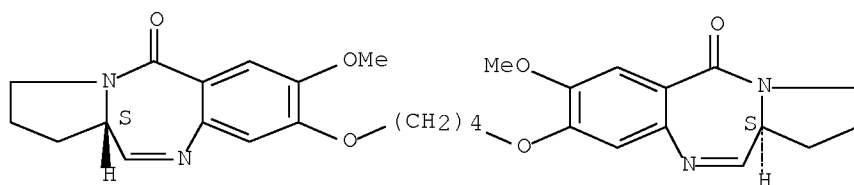
AB A simple and efficient deprotection of thioacetals, e.g., I, has been achieved by employing bismuth triflate. This method has been effectively employed in the preparation of DNA-binding pyrrolo[2,1-c] [1,4]benzodiazepine II and its dimers.  
 IT 140676-21-7P 145325-56-0P 145325-57-1P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (stereoselective preparation of pyrrolobenzodiazepine dimers via dimerization of chiral nitro(hydroxy)benzoylpyrrolidinecarboxaldehyde thioacetal with dibromoalkanes followed by reduction, bismuth-catalyzed deprotection, and heterocyclization)  
 RN 140676-21-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c] [1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 145325-56-0 CAPLUS  
 CN 5H-Pyrrolo[2,1-c] [1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

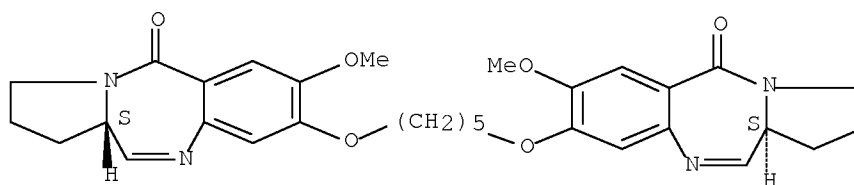
Absolute stereochemistry.



RN 145325-57-1 CAPLUS

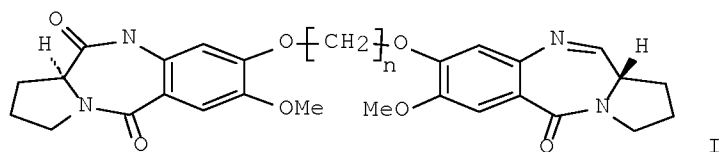
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediyldis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 58 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2002:702235 CAPLUS Full-text  
 DN 138:4582  
 TI Design, Synthesis, and Evaluation of New Noncross-Linking  
 Pyrrolobenzodiazepine Dimers with Efficient DNA Binding Ability and Potent  
 Antitumor Activity  
 AU Kamal, Ahmed; Ramesh, G.; Laxman, N.; Ramulu, P.; Srinivas, O.; Neelima,  
 K.; Kondapi, Anand K.; Sreenu, V. B.; Nagarajaram, H. A.  
 CS Biotransformation Laboratory, Division of Organic Chemistry, Indian  
 Institute of Chemical Technology, Hyderabad, 500 007, India  
 SO Journal of Medicinal Chemistry (2002), 45(21), 4679-4688  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 138:4582  
 GI



AB Pseudodimeric pyrrolobenzodiazepines I ( $n = 3-5, 8$ ) possessing both imine and amide moieties and oxyalkyloxy linkers are prepared and evaluated as DNA-binding compds. for use as potential anticancer agents. I ( $n = 5$ ) binds to calf thymus DNA and increases the melting temperature of the DNA by  $17^\circ$ , comparable or greater than the increase in DNA melting temperature by other DNA binding agents. The length of the linker affects the binding of I significantly; while I ( $n = 5$ ) increases the melting temperature of DNA by  $17^\circ$ , I ( $n = 8$ ) increases the melting temperature of DNA by only  $0.7^\circ$ . I ( $n = 3-5$ ) are tested for their cytotoxicities against a variety of human cancer cell lines; I ( $n = 3-5$ ) kill 50% of the cancer cells at concentration of 10-100  $\mu\text{M}$ . The binding of I ( $n = 3-5, 8$ ) to a 15 base pair sequence of DNA is simulated; the binding affinities calculated correspond well to the exptl. binding affinities, with I ( $n = 5$ ) stabilizing DNA helixes more effectively than I ( $n = 3, 4, 8$ ). The energy of interaction in all of the complexes studied is correlated to the change in DNA melting temperature. Both noncovalent and covalent interactions are important in understanding the affinities of I for DNA and their antitumor activities.

IT 477207-67-3 477207-69-5 477207-98-0  
 477208-74-5

RL: PRP (Properties)

(calculated energies of interaction of oxyalkyloxy-linked pseudodimers of pyrrolo[2,1-c][1,4]benzodiazepines with 15 base pair DNA sequences)

RN 477207-67-3 CAPLUS

CN DNA, d(G-G-G-G-C-G-A-G-A-G-A-G-G-G), compd. with (11aS)-2,3-dihydro-7-methoxy-8-[3-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione (1:1) (9CI) (CA INDEX NAME)

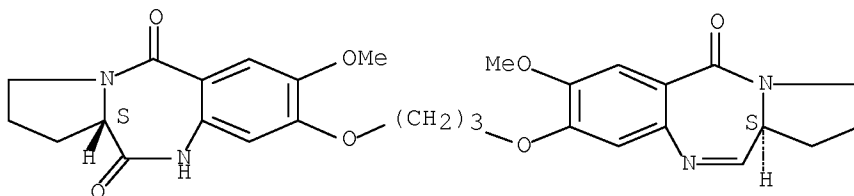
CRN 477207-55-9  
CMF Unspecified  
CCI MAN

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

CM 2

CRN 343308-43-0  
CMF C29 H32 N4 O7

Absolute stereochemistry. Rotation (+).



RN 477207-69-5 CAPLUS  
CN DNA, d(G-G-G-G-C-G-A-G-A-G-A-G-G-G), compd. with (11aS)-2,3-dihydro-7-methoxy-8-[[4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione (1:1) (9CI) (CA INDEX NAME)

CM 1

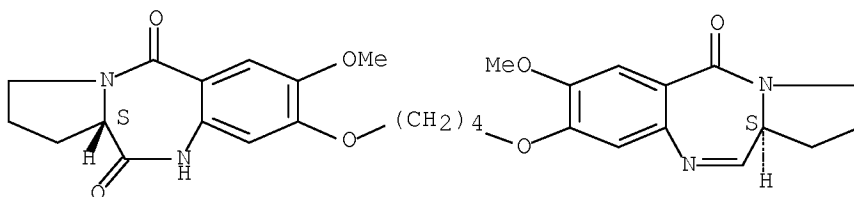
CRN 477207-55-9  
CMF Unspecified  
CCI MAN

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

CM 2

CRN 343308-44-1  
CMF C30 H34 N4 O7

Absolute stereochemistry. Rotation (+).



RN 477207-98-0 CAPLUS  
CN DNA, d(G-G-G-G-C-G-A-G-A-G-A-G-G-G), compd. with (11aS)-2,3-dihydro-7-methoxy-8-[[5-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione (1:1) (9CI) (CA INDEX NAME)

c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-1H-pyrrolo[2,1-  
c][1,4]benzodiazepine-5,11(10H,11aH)-dione (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 477207-55-9

CMF Unspecified

CCI MAN

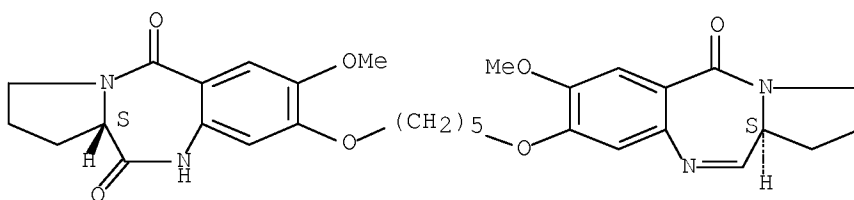
\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

CM 2

CRN 343308-45-2

CMF C31 H36 N4 O7

Absolute stereochemistry. Rotation (+).



RN 477208-74-5 CAPLUS

CN DNA, d(G-G-G-G-C-G-A-G-A-G-A-G-G-G-G), compd. with (11aS)-2,3-dihydro-7-methoxy-8-[[8-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]octyl]oxy]-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 477207-55-9

CMF Unspecified

CCI MAN

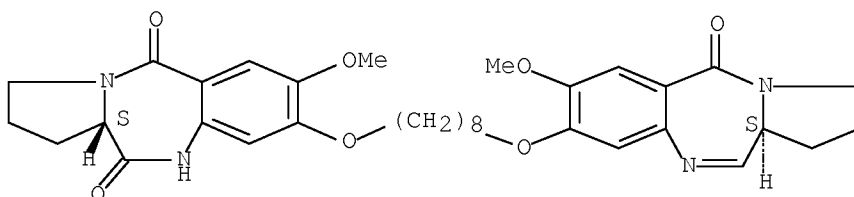
\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

CM 2

CRN 476015-23-3

CMF C34 H42 N4 O7

Absolute stereochemistry. Rotation (+).





IT 343308-43-0D, calf thymus DNA-bound 343308-44-1D, calf  
thymus DNA-bound 343308-45-2D, calf thymus DNA-bound  
476015-23-3D, calf thymus DNA-bound

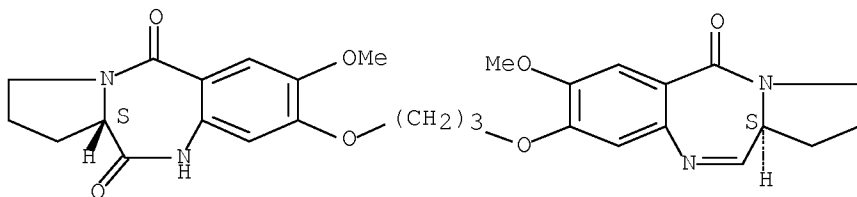
RL: PRP (Properties)

(increase of DNA melting temperature upon binding of oxyalkyloxy-linked  
pseudodimers of pyrrolo[2,1-c][1,4]benzodiazepines to calf thymus DNA)

RN 343308-43-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
2,3-dihydro-7-methoxy-8-[3-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-  
1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (CA INDEX  
NAME)

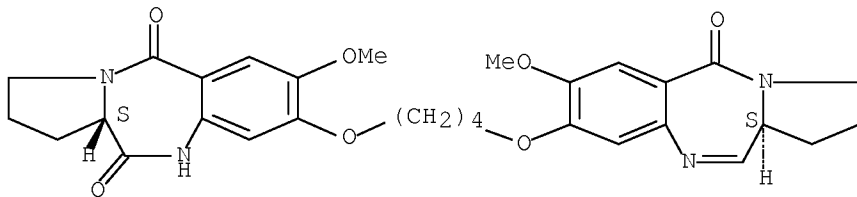
Absolute stereochemistry. Rotation (+).



RN 343308-44-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
2,3-dihydro-7-methoxy-8-[4-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-  
1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (11aS)- (CA INDEX  
NAME)

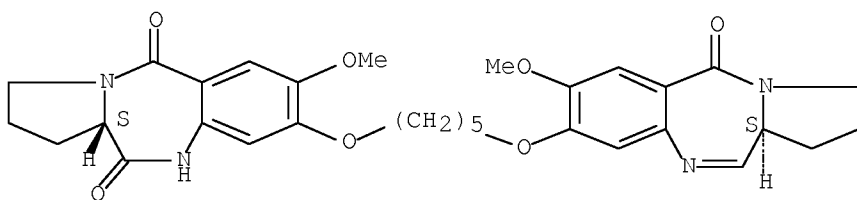
Absolute stereochemistry. Rotation (+).



RN 343308-45-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
2,3-dihydro-7-methoxy-8-[[5-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-  
1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (CA  
INDEX NAME)

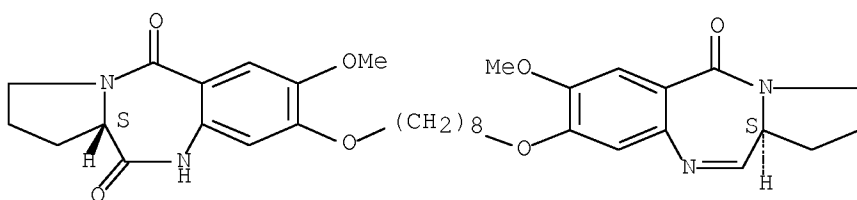
Absolute stereochemistry. Rotation (+).



RN 476015-23-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
2,3-dihydro-7-methoxy-8-[[8-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]octyl]oxy]-, (11aS)- (CA  
INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 343308-43-0P 343308-44-1P 343308-45-2P

476015-23-3P

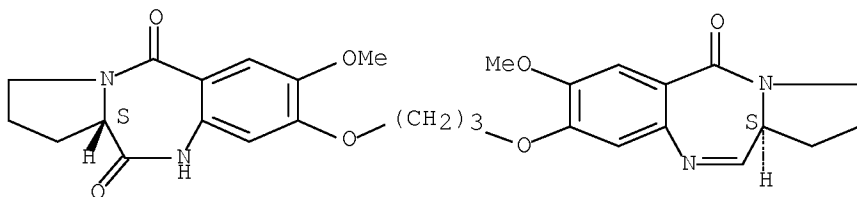
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL  
(Biological study); PREP (Preparation)

(preparation of oxyalkyloxy-linked pseudodimers of pyrrolo[2,1-  
c][1,4]benzodiazepines as DNA binding and antitumor agents)

RN 343308-43-0 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
2,3-dihydro-7-methoxy-8-[3-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (CA INDEX  
NAME)

Absolute stereochemistry. Rotation (+).

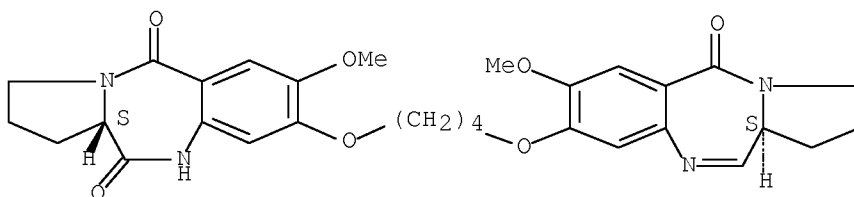


RN 343308-44-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
2,3-dihydro-7-methoxy-8-[4-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-

1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (11aS)- (CA INDEX NAME)

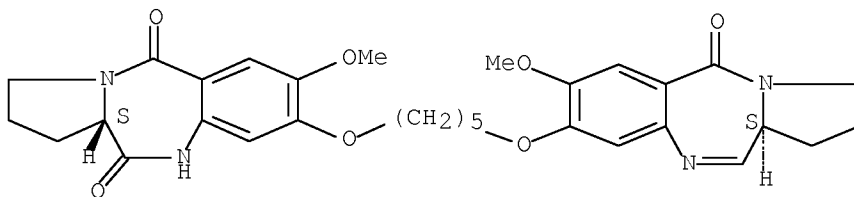
Absolute stereochemistry. Rotation (+).



RN 343308-45-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[[5-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (CA INDEX NAME)

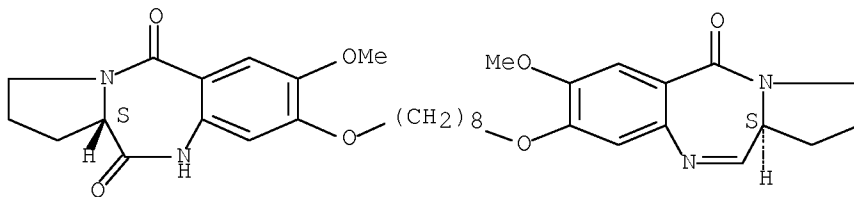
Absolute stereochemistry. Rotation (+).



RN 476015-23-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[[8-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]octyl]oxy]-, (11aS)- (CA INDEX NAME)

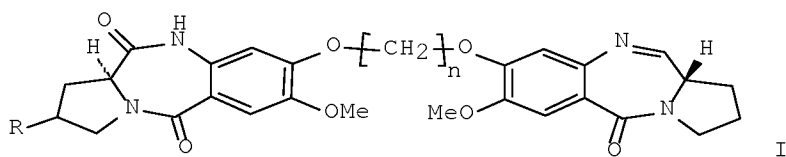
Absolute stereochemistry. Rotation (+).



RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 59 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2002:237375 CAPLUS Full-text  
 DN 136:263030  
 TI Preparation of pyrrolobenzodiazepines as antitumor agents  
 IN Kamal, Ahmed; Nallan, Chakravarthy Laxman; Gujjar, Ramesh; Poddutoori,  
 Ramulu; Olepu, Srinivas  
 PA Council of Scientific and Industrial Research, India  
 SO U.S., 12 pp.  
 CODEN: USXXAM  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6362331	B1	20020326	US 2001-822782	20010330
PRAI	US 2001-822782		20010330		
OS	CASREACT 136:263030; MARPAT 136:263030				
GI					



AB The present invention provides a process for the preparation of a novel pyrrolo[2,1-c][1,4]benzodiazepine of formula I [R = H, OH, OAc; n = 3-5], by reacting (2S)-N-[4-hydroxy-5-methoxy-2-nitrobenzyl]-pyrrolidine-2-carboxaldehyde di-Et thioacetal with a dibromoalkane, isolating (2S)-N-[4-(3-bromoalkoxy)-5-methoxy-2-nitrobenzoyl]pyrrolidine-2-carboxaldehyde di-Et thioacetal so formed and reacting the isolate with a dilactam, isolating 8-[[[(2S)-N-5-methoxy-2-nitrobenzoyl]pyrrolidin-2-carbaldehyde diethylthioacetal]-alkoxy-7-methoxy-2,3,5,10,11,11a-hydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione, reducing the above nitro compound, isolating the 8-[[[(2S)-N-5-methoxy-2-aminobenzoyl]pyrrolidin-2-carbaldehyde diethylthioacetal]-alkoxy-7-methoxy-2,3,5,10,11,11a-hydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione, reacting the amino compound above with a deprotecting agent to obtain the pyrrolo[2,1-c][1,4]benzodiazepines. The pyrrolo[2,1-c][1,4]benzodiazepines are useful as antitumor agents. Thus, II (R = H, n = 5) was prepared as described above and showed significant DNA binding affinity and anticancer activity against three human cell lines.

IT 343308-43-0P 343308-44-1P 343308-45-2P  
 405108-10-3P 405108-11-4P 405108-12-5P  
 405108-13-6P 405108-14-7P 405108-15-8P

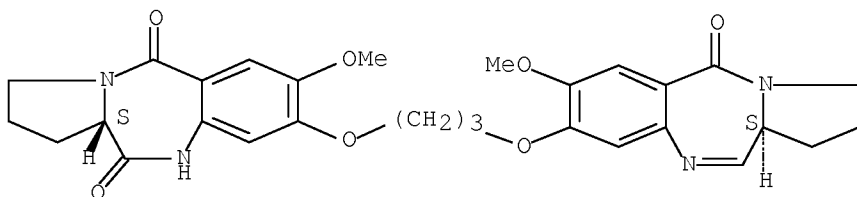
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of pyrrolobenzodiazepines as antitumor agents)

RN 343308-43-0 CAPLUS

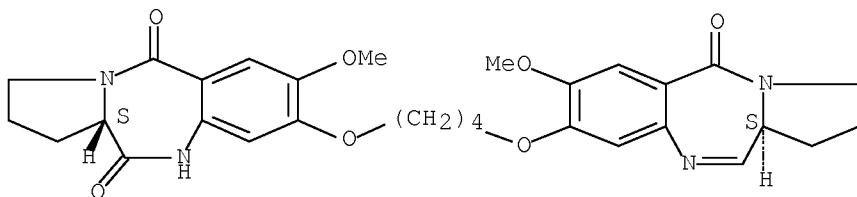
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
 2,3-dihydro-7-methoxy-8-[3-[[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



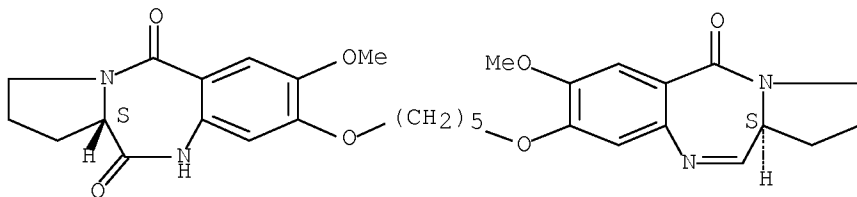
RN 343308-44-1 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
 2,3-dihydro-7-methoxy-8-[4-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-  
 1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (11aS)- (CA INDEX  
 NAME)

Absolute stereochemistry. Rotation (+).



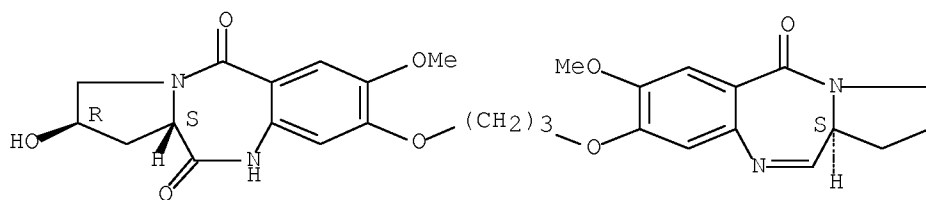
RN 343308-45-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
 2,3-dihydro-7-methoxy-8-[[5-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-  
 1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (CA  
 INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 405108-10-3 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
 2,3-dihydro-2-hydroxy-7-methoxy-8-[3-[[ (11aS)-2,3,5,11a-tetrahydro-7-  
 methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-,  
 (2R,11aS)- (CA INDEX NAME)

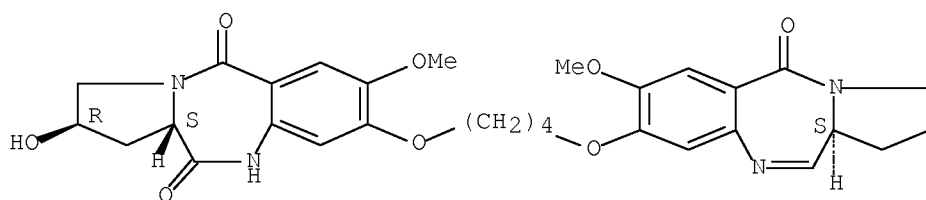
Absolute stereochemistry.



RN 405108-11-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
2,3-dihydro-2-hydroxy-7-methoxy-8-[4-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-,  
(2R,11aS)- (CA INDEX NAME)

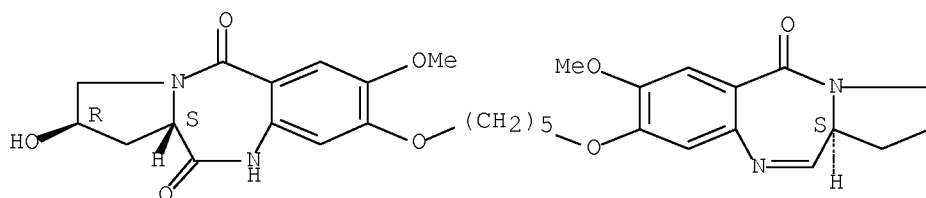
Absolute stereochemistry.



RN 405108-12-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
2,3-dihydro-2-hydroxy-7-methoxy-8-[[5-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-,  
(2R,11aS)- (CA INDEX NAME)

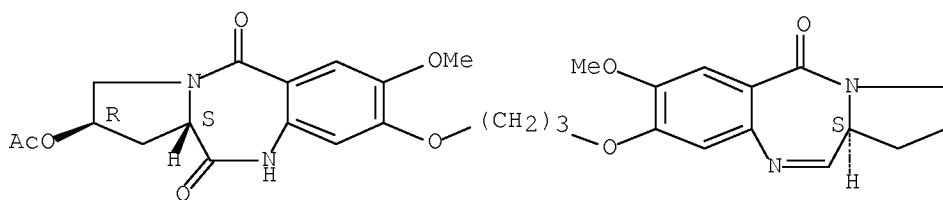
Absolute stereochemistry.



RN 405108-13-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
2-(acetyloxy)-2,3-dihydro-7-methoxy-8-[3-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-,  
(2R,11aS)- (CA INDEX NAME)

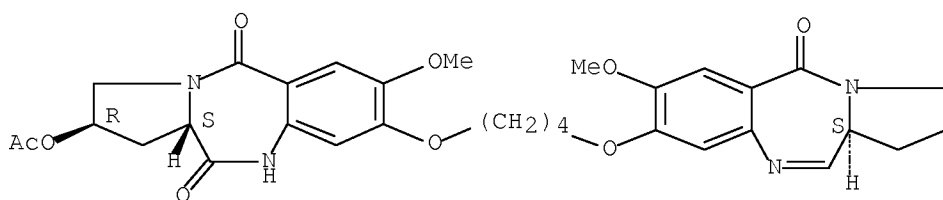
Absolute stereochemistry.



RN 405108-14-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
2-(acetyloxy)-2,3-dihydro-7-methoxy-8-[4-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-,  
(2R,11aS)- (CA INDEX NAME)

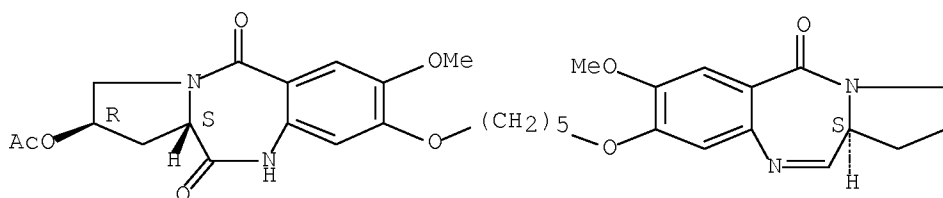
Absolute stereochemistry.



RN 405108-15-8 CAPLUS

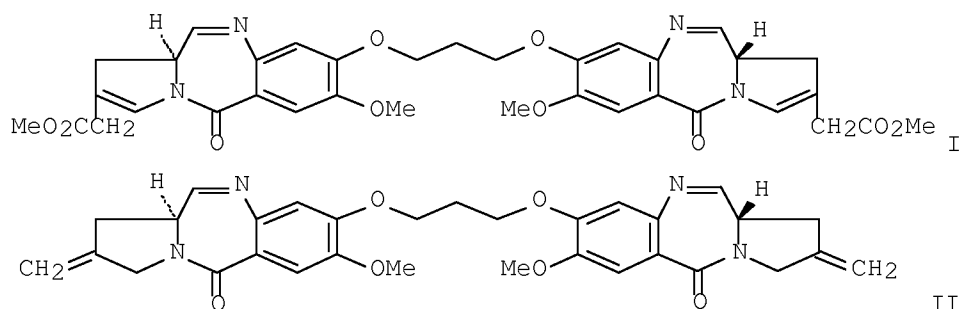
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
2-(acetyloxy)-2,3-dihydro-7-methoxy-8-[[5-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-,  
(2R,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

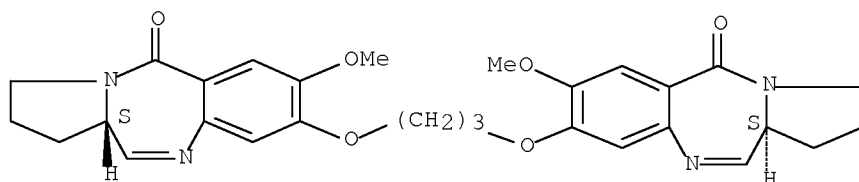
L18 ANSWER 60 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2001:746612 CAPLUS Full-text  
 DN 136:200170  
 TI Synthesis of the first example of a C2-C3/C2'-C3'-endo unsaturated  
 pyrrolo[2,1-c][1,4]benzodiazepine dimer  
 AU Gregson, S. J.; Howard, P. W.; Corcoran, K. E.; Jenkins, T. C.; Kelland,  
 L. R.; Thurston, D. E.  
 CS Cancer Research Laboratories, CRC Gene Targeted Drug Design Research  
 Group, University of Nottingham, School of Pharmaceutical Sciences,  
 Nottingham, NG7 2RD, UK  
 SO Bioorganic & Medicinal Chemistry Letters (2001), 11(21), 2859-2862  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Science Ltd.  
 DT Journal  
 LA English  
 OS CASREACT 136:200170  
 GI



AB We report the first example of a C2-C3/C2'-C3'-endo unsatd. pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimer (I) synthesized through a new and efficient route, thus establishing that C2-C3-endo unsatn. enhances both cytotoxicity and DNA-binding affinity in A-ring-linked PBD dimers but to a lesser extent than C2/C2'-exo-unsatn. This new route has allowed the preparation of multigram quantities of the related clin. candidate II and should lead to more structurally diverse PBD dimer analogs.

IT 140676-21-7  
 RL: PAC (Pharmacological activity); BIOL (Biological study)  
 (preparation of first example of C2-C3/C2'-C3'-endo unsatd.  
 pyrrolo[2,1-c][1,4]benzodiazepine dimer)  
 RN 140676-21-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
 propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
 (CA INDEX NAME)

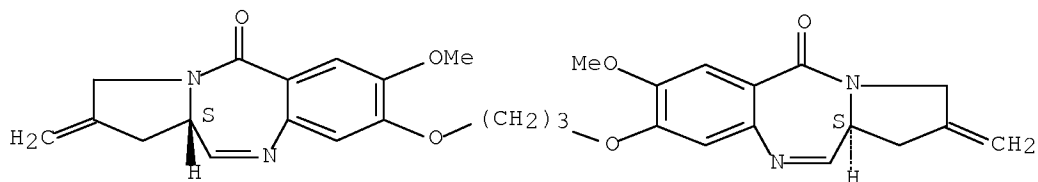
Absolute stereochemistry. Rotation (+).





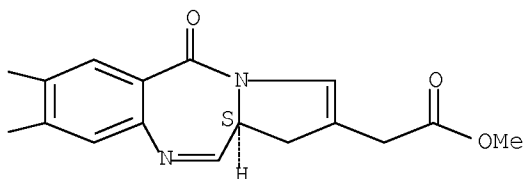
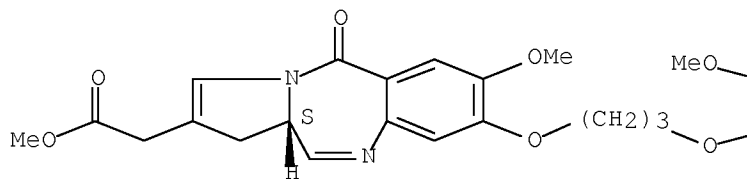
IT 232931-57-6P 260543-81-5P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL  
 (Biological study); PREP (Preparation)  
 (preparation of first example of C2-C3/C2'-C3'-endo unsatd.  
 pyrrolo[2,1-c][1,4]benzodiazepine dimer)  
 RN 232931-57-6 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
 propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-,  
 (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 260543-81-5 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acetic acid, 8,8'-[1,3-  
 propanediylbis(oxy)]bis[5,11a-dihydro-7-methoxy-5-oxo-, dimethyl ester,  
 (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



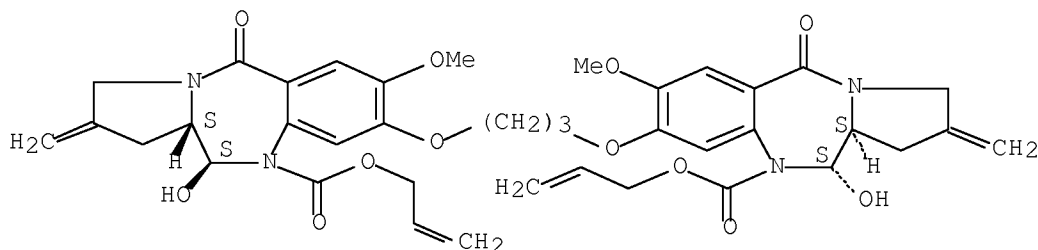
IT 232931-64-5P 260418-01-7P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (preparation of first example of C2-C3/C2'-C3'-endo unsatd.

pyrrolo[2,1-c][1,4]benzodiazepine dimer)

RN 232931-64-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-  
(9CI) (CA INDEX NAME)

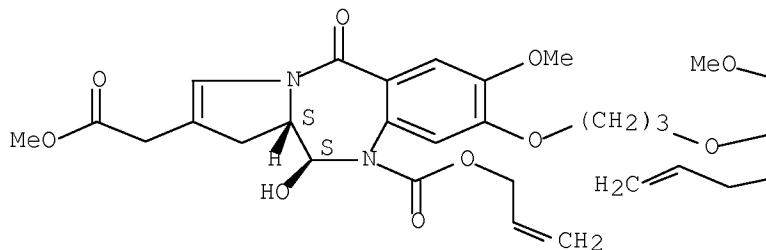
Absolute stereochemistry.



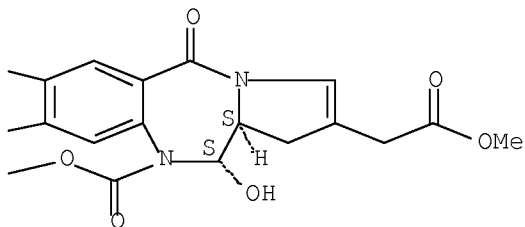
RN 260418-01-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acetic acid, 8,8'-[1,3-  
propanediylbis(oxy)]bis[5,10,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-  
10-[(2-propenyloxy)carbonyl]-, dimethyl ester, (11S,11'S,11aS,11'aS)-  
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



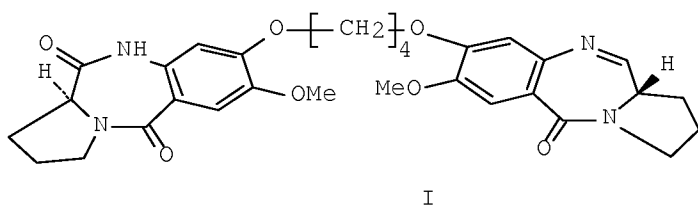
PAGE 1-A



PAGE 1-B

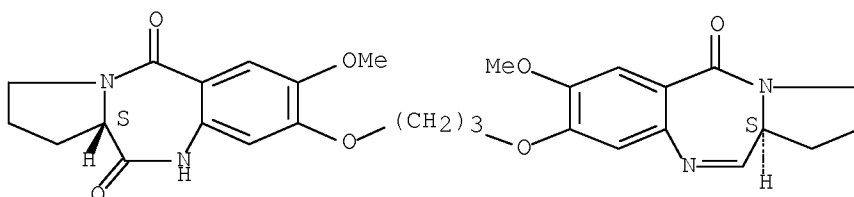
RE.CNT 17      THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 61 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2001:139435 CAPLUS Full-text  
 DN 135:13847  
 TI Synthesis of novel non-cross-linking pyrrolobenzodiazepines with  
 remarkable DNA binding affinity and potent antitumour activity  
 AU Kamal, Ahmed; Laxman, N.; Ramesh, G.; Neelima, K.; Kondapi, Anand K.  
 CS Division of Organic Chemistry, Indian Institute of Chemical Technology,  
 Hyderabad, 500 007, India  
 SO Chemical Communications (Cambridge, United Kingdom) (2001), (5), 437-438  
 CODEN: CHCOFS; ISSN: 1359-7345  
 PB Royal Society of Chemistry  
 DT Journal  
 LA English  
 OS CASREACT 135:13847  
 GI



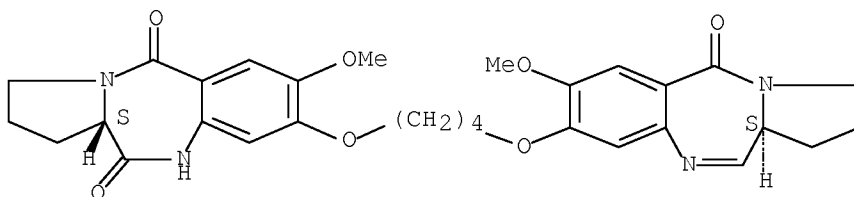
AB Mixed imine-amide pyrrolobenzodiazepine dimers have been prepared which  
 exhibit potent antitumor activity and have significant DNA binding affinity;  
 one of them, I, has been shown to cause a remarkable rise in the melting  
 temperature of calf thymus DNA.  
 IT 343308-43-0P 343308-44-1P 343308-45-2P  
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological  
 process); BSU (Biological study, unclassified); SPN (Synthetic  
 preparation); THU (Therapeutic use); BIOL (Biological study); PREP  
 (Preparation); PROC (Process); USES (Uses)  
 (pyrrolobenzodiazepines with DNA binding affinity and antitumor  
 activity)  
 RN 343308-43-0 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
 2,3-dihydro-7-methoxy-8-[3-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-  
 1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (CA INDEX  
 NAME)

Absolute stereochemistry. Rotation (+).



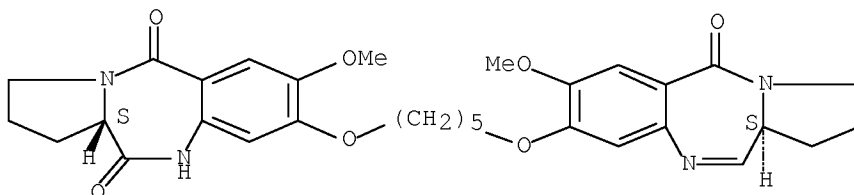
RN 343308-44-1 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
 2,3-dihydro-7-methoxy-8-[4-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-  
 1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (11aS)- (CA INDEX  
 NAME)

Absolute stereochemistry. Rotation (+).



RN 343308-45-2 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
 2,3-dihydro-7-methoxy-8-[[5-[[ (11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-  
 1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (CA  
 INDEX NAME)

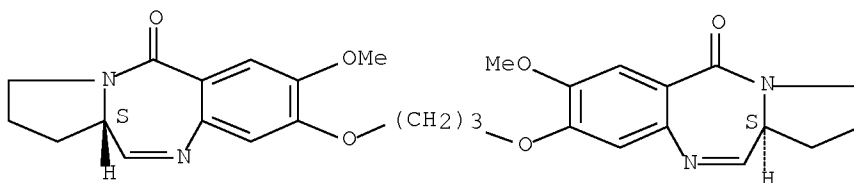
Absolute stereochemistry. Rotation (+).



IT 140676-21-7, DSB 120  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL  
 (Biological study); PROC (Process)  
 (pyrrolobenzodiazepines with DNA binding affinity and antitumor  
 activity)

RN 140676-21-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
 propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
 (CA INDEX NAME)

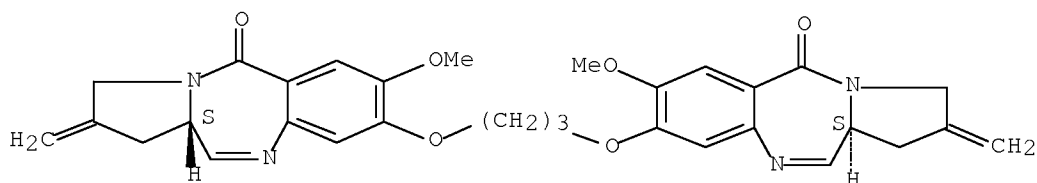
Absolute stereochemistry. Rotation (+).



RE.CNT 17      THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 62 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2001:68712 CAPLUS Full-text  
 DN 134:260871  
 TI Design, synthesis, and evaluation of a novel pyrrolobenzodiazepine  
 DNA-interactive agent with highly efficient cross-linking ability and  
 potent cytotoxicity  
 AU Gregson, Stephen J.; Howard, Philip W.; Hartley, John A.; Brooks, Natalie  
 A.; Adams, Lesley J.; Jenkins, Terence C.; Kelland, Lloyd R.; Thurston,  
 David E.  
 CS CRC Gene Targeted Drug Design Research Group, Cancer Research Laboratories  
 University of Nottingham, Nottingham, NG7 2RD, UK  
 SO Journal of Medicinal Chemistry (2001), 44(5), 737-748  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 134:260871  
 AB A novel sequence-selective pyrrolobenzodiazepine (PBD) dimer 5 (SJG-136) has  
 been developed that comprises two C2-exo-methylene-substituted DC-81 (3)  
 subunits tethered through their C8 positions via an inert propanedioxy linker.  
 This sym. mol. is a highly efficient minor groove interstrand DNA crosslinking  
 agent (XL50 = 0.045  $\mu$ M) that is 440-fold more potent than melphalan. Thermal  
 denaturation studies show that, after 18 h incubation with calf thymus DNA at  
 a 5:1 DNA/ligand ratio, it increases the T<sub>m</sub> value by 33.6°, the highest value  
 so far recorded in this assay. The analogous dimer 4 (DSB-120) that lacks  
 substitution/unsatn. at the C2 position elevates melting by only 15.1° under  
 the same conditions, illustrating the effect of introducing C2-exo-unsatn.  
 which serves to flatten the C-rings and achieve a superior isohelical fit  
 within the DNA minor groove. This behavior is supported by mol. modeling  
 studies which indicate that (i) the PBD units are covalently bonded to  
 guanines on opposite strands to form a cross-link, (ii) 5 has a greater  
 binding energy compared to 4, and (iii) 4 and 5 have equivalent binding sites  
 that span six base pairs. Dimer 5 is significantly more cytotoxic than 4 in a  
 number of human ovarian cancer cell lines (e.g., IC<sub>50</sub> values of 0.0225 nM vs.  
 7.2 nM, resp., in A2780 cells). Furthermore, it retains full potency in the  
 cisplatin-resistant cell line A2780cisR (0.024 nM), whereas 4 loses activity  
 (0.21  $\mu$ M) with a resistance factor of 29.2. This may be due to a lower level  
 of inactivation of 5 by intracellular thiol-containing mols. A dilactam  
 analog, tetralactam of 5 that lacks the electrophilic N10-C11/N10'-C11' imine  
 moieties has also been synthesized and evaluated. Although unable to interact  
 covalently with DNA, tetralactam still stabilizes the helix ( $\Delta$ T<sub>m</sub> = 0.78°) and  
 has significant cytotoxicity in some cell lines (i.e., IC<sub>50</sub> = 0.57  $\mu$ M in CH1  
 cells), presumably exerting its effect through noncovalent interaction with  
 DNA.  
 IT 232931-57-6P 232931-67-8P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);  
 BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (design, synthesis, and evaluation of a novel pyrrolobenzodiazepine  
 DNA-interactive agent with highly efficient crosslinking ability and  
 potent cytotoxicity)  
 RN 232931-57-6 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
 propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-,  
 (11aS,11'aS)- (CA INDEX NAME)

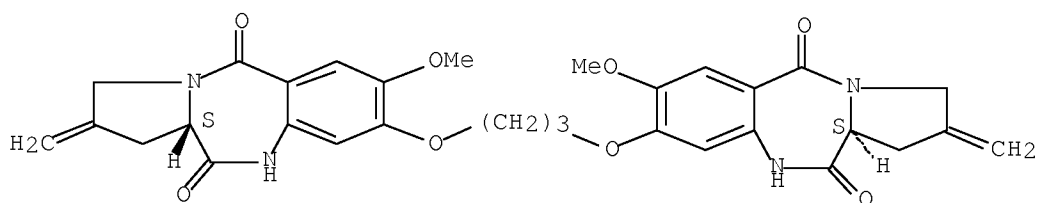
Absolute stereochemistry. Rotation (+).



RN 232931-67-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
8,8'-[1,3-propanediylbis(oxy)]bis[2,3-dihydro-7-methoxy-2-methylene-,  
(11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 140676-21-7

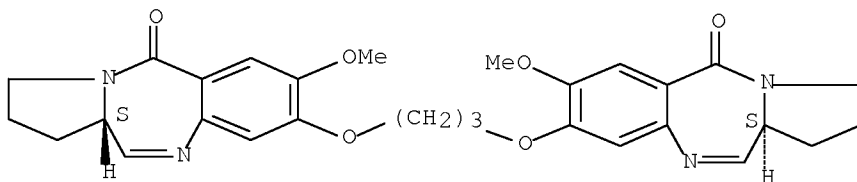
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(design, synthesis, and evaluation of a novel pyrrolobenzodiazepine DNA-interactive agent with highly efficient crosslinking ability and potent cytotoxicity)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 232931-64-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

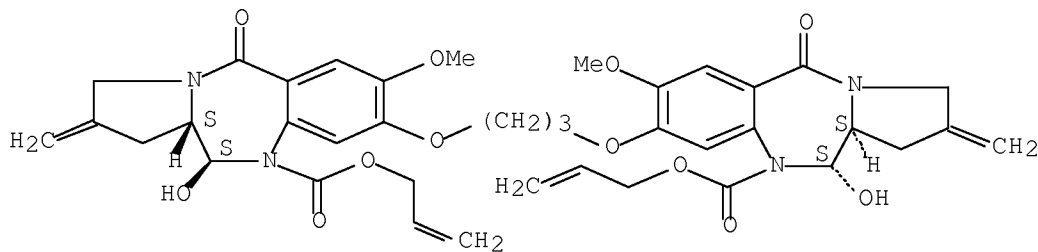
(design, synthesis, and evaluation of a novel pyrrolobenzodiazepine DNA-interactive agent with highly efficient crosslinking ability and potent cytotoxicity)

RN 232931-64-5 CAPLUS



CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
 methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-  
 (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 63 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2000:845290 CAPLUS Full-text

DN 134:131508

TI Reductive cyclization of  $\omega$ -azido/nitro carbonyl compounds by samarium iodide: a facile preparation of DNA-binding pyrrolo[2,1-c][1,4]benzodiazepine and its dimers

AU Kamal, Ahmed; Laxman, E.; Reddy, P. S. M. M.

CS Division of Organic Chemistry-I, Indian Institute of Chemical Technology, Hyderabad, 500 007, India

SO Tetrahedron Letters (2000), 41(44), 8631-8634

CODEN: TELEAY; ISSN: 0040-4039

PB Elsevier Science Ltd.

DT Journal

LA English

OS CASREACT 134:131508

AB An efficient synthesis of pyrrolo[2,1-c][1,4]benzodiazepines via reductive cyclization of  $\omega$ -azido/nitro carbonyl compds. employing SmI<sub>2</sub> is described. This methodol. was extended for the preparation of DNA-crosslinking DC-81 dimers.

IT 140676-21-7P 145325-56-0P 145325-57-1P

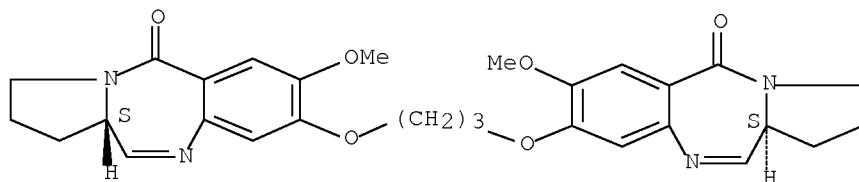
RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of pyrrolo[2,1-c][1,4]benzodiazepine dimers by reductive cyclization of  $\omega$ -azido/nitro carbonyls with samarium iodide)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

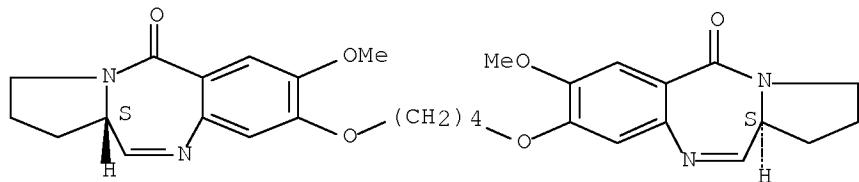
Absolute stereochemistry. Rotation (+).



RN 145325-56-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry.

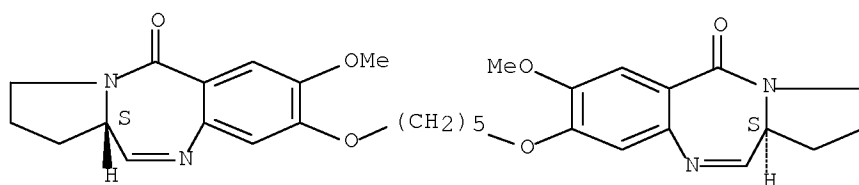


RN 145325-57-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-

pentanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
(CA INDEX NAME)

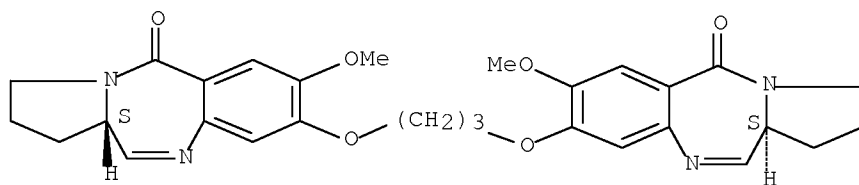
Absolute stereochemistry. Rotation (+).



RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

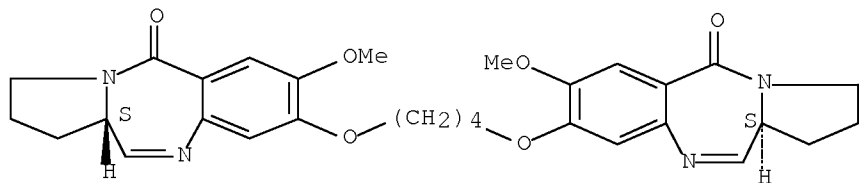
L18 ANSWER 64 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2000:737795 CAPLUS Full-text  
 DN 134:42112  
 TI A mild and efficient dethioacetalization employing FeCl<sub>3</sub>·6H<sub>2</sub>O: synthesis of DNA-binding pyrrolo[2,1-c][1,4]benzodiazepine ring system and its dimers  
 AU Kamal, Ahmed; Laxman, E.; Reddy, P. S. M. M.  
 CS Division of Organic Chemistry-1, Indian Institute of Chemical Technology, Hyderabad, 500 007, India  
 SO Synlett (2000), (10), 1476-1478  
 CODEN: SYNLES; ISSN: 0936-5214  
 PB Georg Thieme Verlag  
 DT Journal  
 LA English  
 OS CASREACT 134:42112  
 AB A simple and efficient dethioacetalization was carried out by employing FeCl<sub>3</sub>·6H<sub>2</sub>O under mild conditions. This method was investigated for the synthesis of DNA-interactive pyrrolo[2,1-c][1,4]benzodiazepine antitumor antibiotics including DC-81 via deprotective cyclization process.  
 IT 140676-21-7P 145325-56-0P 145325-57-1P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of pyrrolo[2,1-c][1,4]benzodiazepines and dimers via dethioacetalization with ferric chloride hydrate)  
 RN 140676-21-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 145325-56-0 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

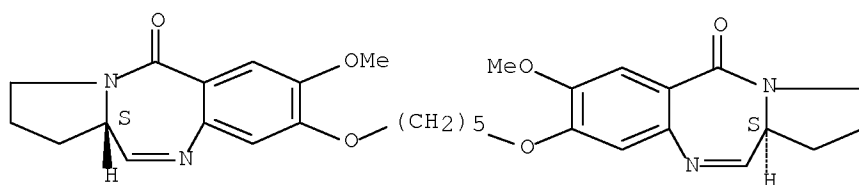
Absolute stereochemistry.



RN 145325-57-1 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-

pentanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
(CA INDEX NAME)

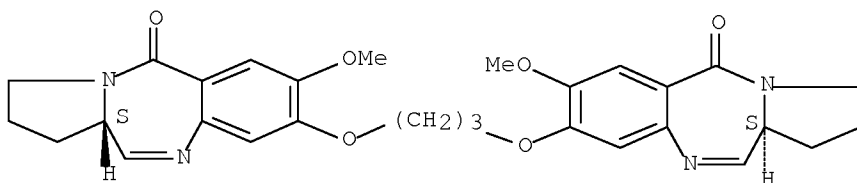
Absolute stereochemistry. Rotation (+).



RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

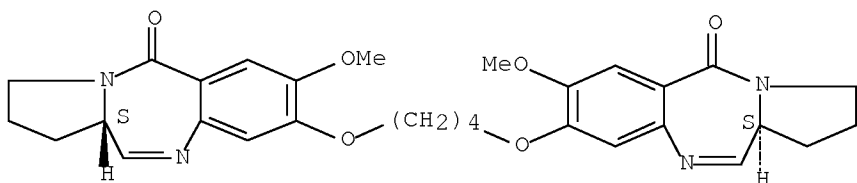
L18 ANSWER 65 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2000:719703 CAPLUS Full-text  
 DN 134:56501  
 TI Synthesis of pyrrolo[2,1-c][1,4]benzodiazepines via reductive cyclization of  $\omega$ -azido carbonyl compounds by TMSI: an efficient preparation of antibiotic DC-81 and its dimers  
 AU Kamal, A.; Laxman, E.; Laxman, N.; Venugopal Rao, N.  
 CS Division of Organic Chemistry-I, Indian Institute of Chemical Technology, Hyderabad, 500 007, India  
 SO Bioorganic & Medicinal Chemistry Letters (2000), 10(20), 2311-2313  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Science Ltd.  
 DT Journal  
 LA English  
 OS CASREACT 134:56501  
 AB  $\omega$ -Azido carbonyl compds. on reaction with trimethylsilyl iodide (in situ prepared from TMSCl/NaI) led to the formation of diazepine imines in good yields under mild conditions. This methodol. has been applied to the parent unsubstituted pyrrolobenzodiazepine, the natural product DC-81 and its dimers.  
 IT 140676-21-7P 145325-56-0P 145325-57-1P  
 313644-35-8P 313644-44-9P 313644-45-0P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (efficient synthesis of antibiotic DC-81 and its dimers via reductive cyclization of  $\omega$ -azido carbonyl compds. by TMSI)  
 RN 140676-21-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 145325-56-0 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

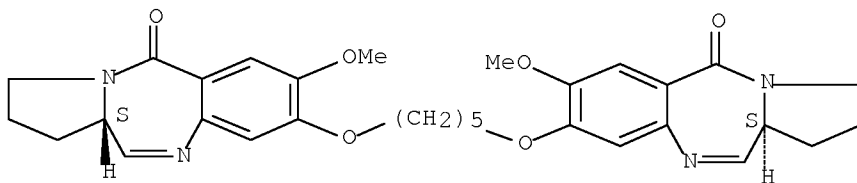
Absolute stereochemistry.



RN 145325-57-1 CAPLUS

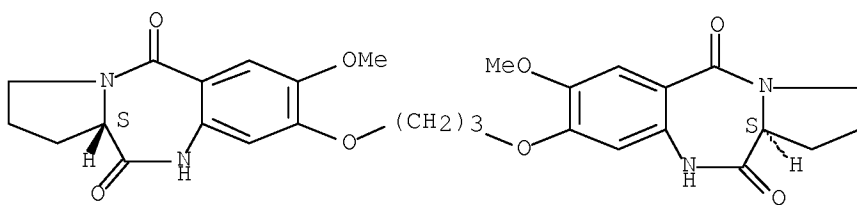
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediy]bis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



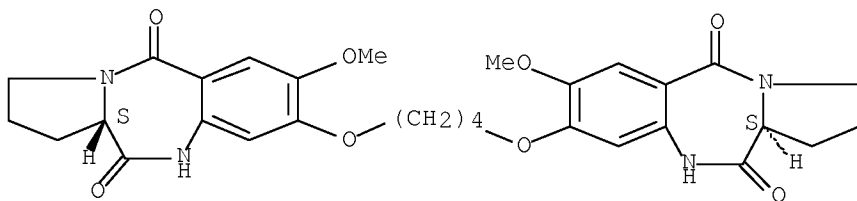
RN 313644-35-8 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 8,8'-[1,3-propanediy]bis(oxy)]bis[2,3-dihydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



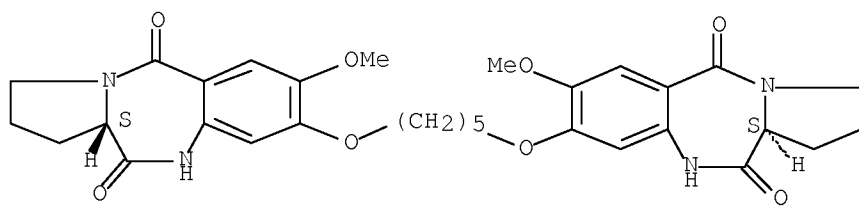
RN 313644-44-9 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 8,8'-[1,4-butanediy]bis(oxy)]bis[2,3-dihydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 313644-45-0 CAPLUS  
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 8,8'-[1,5-pentanediy]bis(oxy)]bis[2,3-dihydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 33      THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



L18 ANSWER 66 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2000:619247 CAPLUS Full-text

DN 133:362758

TI Design and synthesis of novel pyrrolobenzodiazepine (PBD) prodrugs for ADEPT and GDEPT

AU Sagnou, M. J.; Howard, P. W.; Gregson, S. J.; Eno-Amooquaye, E.; Burke, P. J.; Thurston, D. E.

CS School of Pharmacy and Biomedical Sciences, CRC Gene Targeting Drug Design Research Group, University of Portsmouth, Hants, PO1 2DT, UK

SO Bioorganic & Medicinal Chemistry Letters (2000), 10(18), 2083-2086  
CODEN: BMCLE8; ISSN: 0960-894X

PB Elsevier Science Ltd.

DT Journal

LA English

OS CASREACT 133:362758

AB Three N10-(4-nitrobenzyl)carbamate-protected PBD prodrugs were prepared and evaluated for potential use in nitro reductase-based ADEPT (antibody-directed enzyme chemotherapy) and GDEPT (gene-directed chemotherapy). For example, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid (4-nitrophenyl)methyl ester was prepared, which is a prodrug precursor to benzyl DC 81. An approx. 100-fold activation was observed for benzyl DC 81.

IT 307925-16-2P

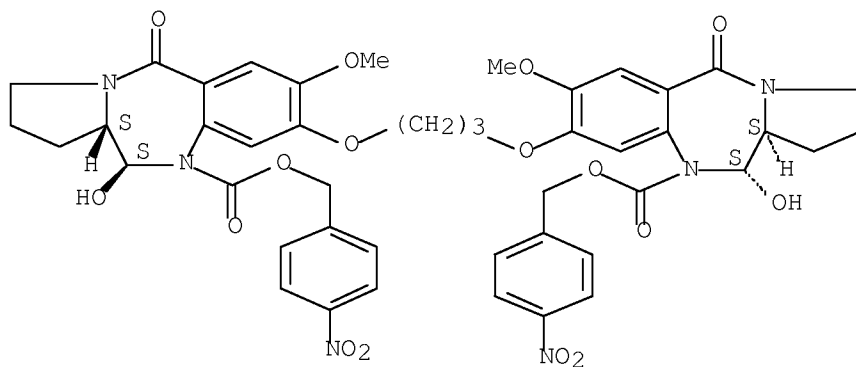
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)

(preparation of pyrrolobenzodiazepine prodrugs for antibody-directed enzyme chemotherapy (ADEPT) and gene-directed enzyme chemotherapy (GEDEPT))

RN 307925-16-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis[(4-nitrophenyl)methyl] ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 307925-17-3P

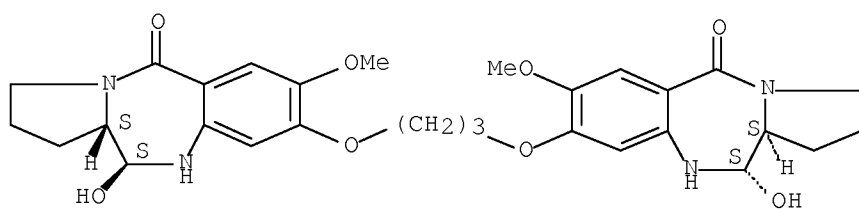
RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of pyrrolobenzodiazepine prodrugs for antibody-directed enzyme chemotherapy (ADEPT) and gene-directed enzyme chemotherapy (GEDEPT))

RN 307925-17-3 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-11-hydroxy-7-methoxy-, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 67 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2000:161284 CAPLUS Full-text

DN 132:207851

TI Preparation of pyrrolobenzodiazepines (PBDs) as antitumor agents

IN Thurston, David Edwin; Howard, Philip Wilson

PA The University of Portsmouth Higher Education Corporation, UK

SO PCT Int. Appl., 258 pp.

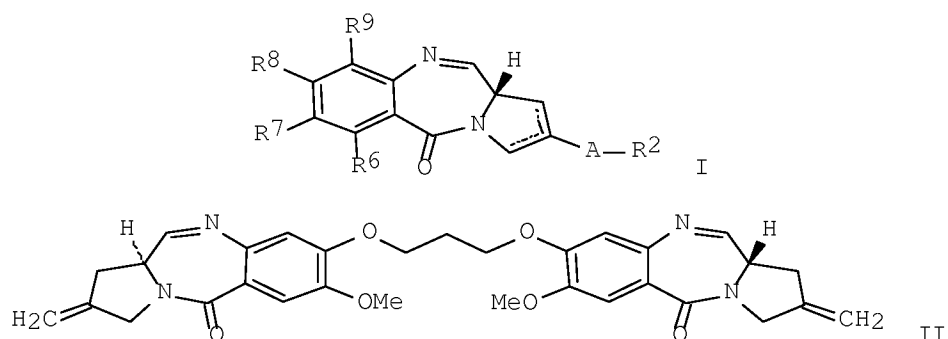
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 2000012508	A2	20000309	WO 1999-GB2838	19990827
	WO 2000012508	A3	20000921		
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	AU 9956351	A	20000321	AU 1999-56351	19990827
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	AT 240334	T	20030515	AT 2001-129700	19990827
	PT 1193270	T	20031031	PT 2001-129700	19990827
	NZ 510493	A	20031128	NZ 1999-510493	19990827
	ES 2199200	T3	20040216	ES 2001-129700	19990827
	EP 1413582	A1	20040428	EP 2003-28817	19990827
	EP 1413582	B1	20060315		
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	AT 294803	T	20050515	AT 1999-943066	19990827
	PT 1109812	T	20050930	PT 1999-943066	19990827
	ES 2244210	T3	20051201	ES 1999-943066	19990827
	AT 320436	T	20060415	AT 2003-28817	19990827
	PT 1413582	T	20060731	PT 2003-28817	19990827
	ES 2260570	T3	20061101	ES 2003-28817	19990827
	US 7049311	B1	20060523	US 2001-763767	20010226
	US 20030120069	A1	20030626	US 2001-21213	20011212
	US 7067511	B2	20060627		
	US 20060148788	A1	20060706	US 2006-367241	20060302
	US 7265105	B2	20070904		
PRAI	GB 1998-18733	A	19980827		
	GB 1999-1929	A	19990128		
	EP 1999-943066	A3	19990827		
	WO 1999-GB2838	W	19990827		
	US 2001-763767	A1	20010226		



AB 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one derivs. (I) [wherein A = CH<sub>2</sub> or a single bond; R = (un)substituted (ar)alkyl, (ar)alkenyl, or (ar)alkynyl; R<sub>2</sub> = R, OH, OR, CO<sub>2</sub>H, CO<sub>2</sub>R, COH, COR, SO<sub>2</sub>R, CN; R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, and R<sub>9</sub> = independently H, R, OH, OR, halo, NH<sub>2</sub>, NHR, NO<sub>2</sub>, SnMe<sub>3</sub>; or the compound is a dimer with each monomer being the same or different and being of formula I and the R<sub>8</sub> groups of the monomers form a -X-R'-X- bridge, where R' is an alkylene chain which may contain ≥ 1 heteroatoms and/or aromatic rings and/or carbon-carbon double or triple bonds, and each X = independently O, S, or N] were prepared for the treatment of gene-based diseases, e.g. neoplastic diseases and Alzheimer's disease, and also bacterial, parasitic, and viral infections. For example, II was synthesized in a 6-step sequence. 1',3'-Bis(4-carboxy-2-methoxy-5-nitrophenoxy)propane (preparation given) was bisamidated with (2S)-2-(tert-butylidimethylsilyloxymethyl)-4-methylenepyrrolidine (74%). TBAF-mediated cleavage of the silyl protecting groups (94%), followed by reduction of the nitro groups by NH<sub>2</sub>NH<sub>2</sub> in the presence of Raney Ni (63%) and N-acylation with allyl chloroformate (50%), gave the protected diamine. Ring closure was accomplished under Swern oxidation conditions, (COCl)<sub>2</sub>-DMSO and TEA, (32%). Finally, the imine was formed from the carbinolamine by N-deprotection using Pd(PPh<sub>3</sub>)<sub>4</sub> and elimination of H<sub>2</sub>O (77%). Both large scale in vitro cytotoxicity cell screens and in vivo hollow fiber and human tumor xenograft assays were performed on selected compds. of the invention. For instance, II exhibited potent and selective cytotoxicity against the lung cancer cell line NCI-H460, the colon cell line HCC-2998, the CNS cancer cell line SNB-75, and the melanoma cell lines MALME-3M (very potent, 0.08 μM) and UACC-62 (very potent, 0.07 μM). In human xenograft studies against five types of tumors, II demonstrated anticancer activity with mixed toxicity results. In addition, II was shown to be the most potent DNA-stabilizing agent known to date according to a DNA helix melting temperature assay. The IC<sub>50</sub> value for II in the A2780 human ovarian carcinoma cell line was only 23 pM, a 320-fold increase in cytotoxicity compared to the known antitumor agent DSB-120 (IC<sub>50</sub> = 5.2 nM). Remarkably, II was also almost 9000-fold more potent in the cisplatin-resistant A2780cisR cell line (IC<sub>50</sub> = 24 pM) than DSB-120 (IC<sub>50</sub> = 0.21 mM), suggesting that II may have potential in the treatment of cisplatin-refractory disease.

IT 232931-64-5P 260418-01-7P 260418-31-3P  
260418-44-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

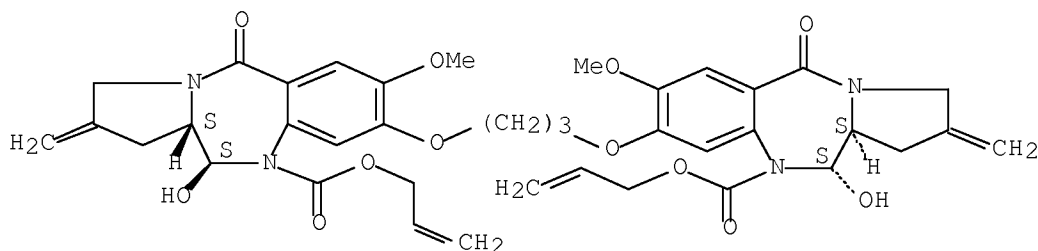
(Reactant or reagent)

(intermediate; preparation of 5H-pyrrolo[2,1-c][1,4]benzodiazepine-5-one antitumor agents from 2-amino- or 2-nitrobenzoic acid derivs. and pyrrolidines)

RN 232931-64-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

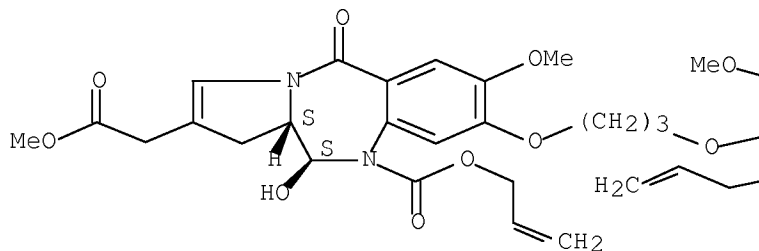


RN 260418-01-7 CAPLUS

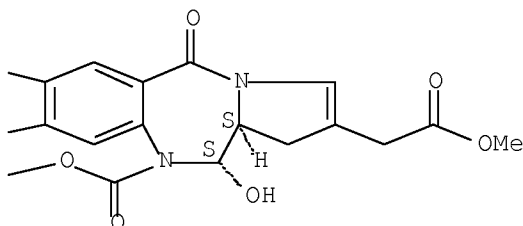
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acetic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[5,10,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-10-[(2-propenyloxy)carbonyl]-, dimethyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

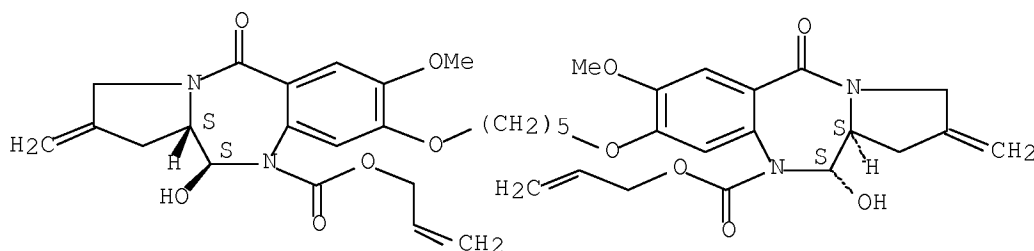


PAGE 1-B



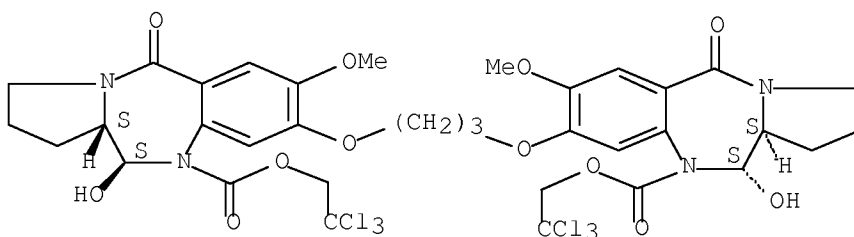
RN 260418-31-3 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,5-pentanediy]bis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
 methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-  
 (9CI) (CA INDEX NAME)

Absolute stereochemistry.



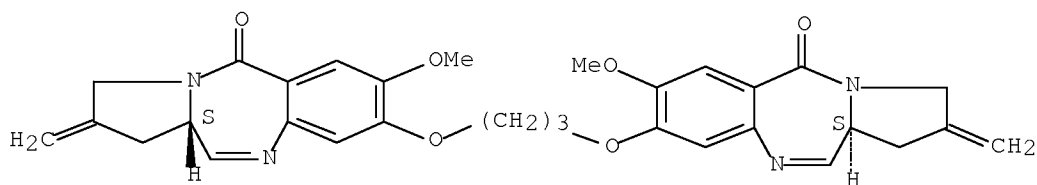
RN 260418-44-8 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediy]bis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-  
 methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)-  
 (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 232931-57-6P, SJG 136  
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or  
 effector, except adverse); BSU (Biological study, unclassified); SPN  
 (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);  
 PREP (Preparation); USES (Uses)  
 (target compound; preparation of 5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one  
 antitumor agents from 2-amino- or 2-nitrobenzoic acid derivs. and  
 pyrrolidines)  
 RN 232931-57-6 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
 propanediy]bis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-,  
 (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



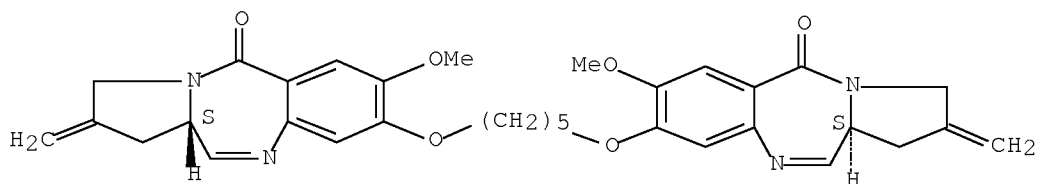
IT 260417-62-7P 260543-81-5P, KEC 570 260546-09-6P  
, DRH 165

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(target compound; preparation of 5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one antitumor agents from 2-amino- or 2-nitrobenzoic acid derivs. and pyrrolidines)

RN 260417-62-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediy]bis(oxy)bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

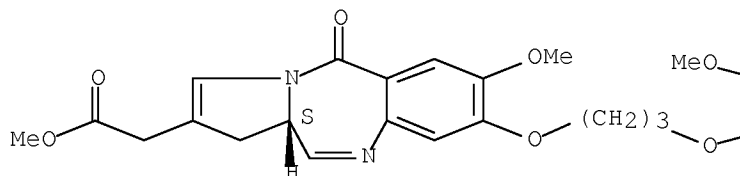


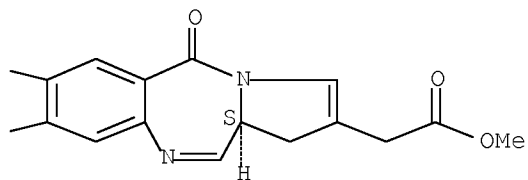
RN 260543-81-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-2-acetic acid, 8,8'-[1,3-propanediyl]bis(oxy)bis[5,11a-dihydro-7-methoxy-5-oxo-, dimethyl ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

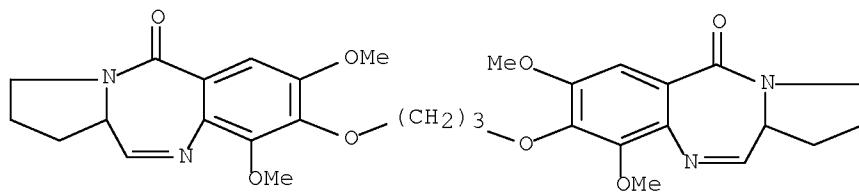




RN 260546-09-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7,9-dimethoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.





L18 ANSWER 68 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2000:161283 CAPLUS Full-text

DN 132:207703

TI Preparation of pyrrolobenzodiazepines (PBDs) as antitumor antibiotics

IN Thurston, David Edwin; Howard, Philip Wilson

PA The University of Portsmouth Higher Education Corporation, UK

SO PCT Int. Appl., 101 pp.

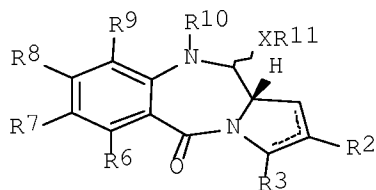
CODEN: PIXXD2

DT Patent

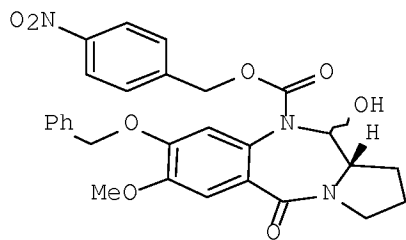
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 2000012507	A2	20000309	WO 1999-GB2837	19990827
	WO 2000012507	A3	20000831		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2341968	A1	20000309	CA 1999-2341968	19990827
	AU 9955261	A1	20000321	AU 1999-55261	19990827
	AU 758398	B2	20030320		
	EP 1109811	A2	20010627	EP 1999-941766	19990827
	EP 1109811	B1	20030806		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002525284	T	20020813	JP 2000-571053	19990827
	AT 246687	T	20030815	AT 1999-941766	19990827
	NZ 510492	A	20030829	NZ 1999-510492	19990827
	PT 1109811	T	20031231	PT 1999-941766	19990827
	ES 2205872	T3	20040501	ES 1999-941766	19990827
	US 6562806	B1	20030513	US 2001-763814	20010226
	US 20030195196	A1	20031016	US 2003-379049	20030304
PRAI	GB 1998-18731	A	19980827		
	WO 1999-GB2837	W	19990827		
	US 2001-763814	A1	20010226		
OS	MARPAT 132:207703				
GI					



I



II

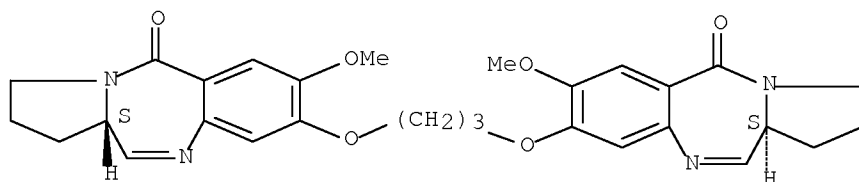
AB 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one derivs. (I) [wherein R = (un)substituted (ar)alkyl, etc.; R2 and R3 = independently H, R, OH, OR, =O, =CH-R, =CH2, CH2-CO2R, CH2-CO2H, CH2-SO2R, O-SO2-R, CO2R, COR, or CN; R6, R7, R8, and R9 = independently H, R, OH, OR, halo, NH2, NO2, or Me3Sn; or R7 and R8 together form a -O-(CH2)p-O- group, where p = 1 or 2; or the compound is a dimer with each monomer being the same or different and being of formula I and the R8 groups of the monomers form a -T-R'-T- bridge, where R' is an alkylene chain which may contain  $\geq 1$  heteroatoms and/or aromatic rings and/or carbon-carbon double or triple bonds, and each T = independently O, S, or N; R10 = a therapeutically removable N-protecting group; R11 = H or R; X is S, O, or NH] were prepared for the treatment of cancer and other site-specific diseases where a local increase of toxicity is beneficial to the patient. Examples include the syntheses of benzyl DC-81, benzyl tomaymycin, and DSB-120 prodrugs starting from 2-nitrobenzoic acid derivs. and pyrrolidines. Data from enzyme and light activation studies and cytotoxicity assays are also given. For example, the nitroreductase-activated benzyl DC-81 (II) was formed in a 6-step sequence involving: (1) benzylation of vanillic acid (67%); (2) ring nitration (82%); (3) amidation with (2S)-pyrrolidinemethanol (88%); (4) reduction of the nitro group (81%); (5) N-addition of 4-nitrobenzyl chloroformate; and (6) cyclization using Swern oxidation conditions (31%). In the presence of nitroreductase and the NADH co-factor, II demonstrated antitumor activity (IC50 = 1-5  $\mu$ M) against the SW1116 and LS174T human adenocarcinoma colonic cell lines. II proved non-toxic in SW1116 cells at concns.  $\leq$  500  $\mu$ M and showed slight toxicity in LS174T cells at concns.  $>$  100  $\mu$ M. I may also be suitable for treating bacterial, parasitic, or viral infections by exploiting a unique enzyme produced at the site of infection which is not natural to the host, or by exploiting an elevation in the amount of an enzyme which does occur naturally in the host.

IT 140676-21-7, DSB 120  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (preparation of pyrrolobenzodiazepinone prodrugs from 2-nitrobenzoic acid derivs. and pyrrolidines for the treatment of cancer)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

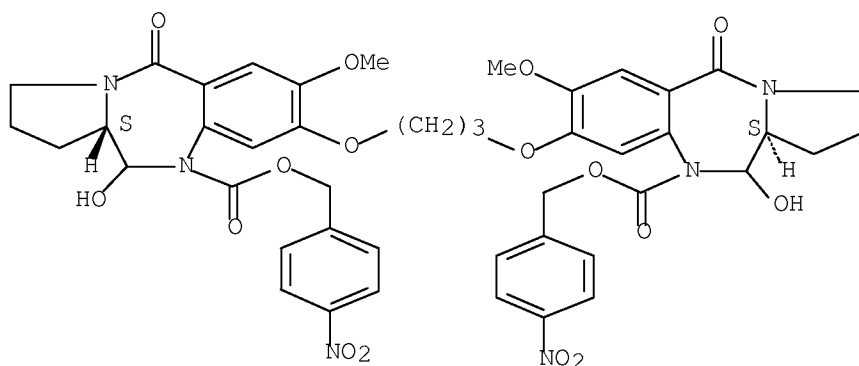
Absolute stereochemistry. Rotation (+).



IT 260391-43-3P 260391-44-4P 260391-45-5P  
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (target compound; preparation of pyrrolobenzodiazepinone prodrugs from 2-nitrobenzoic acid derivs. and pyrrolidines for the treatment of cancer)

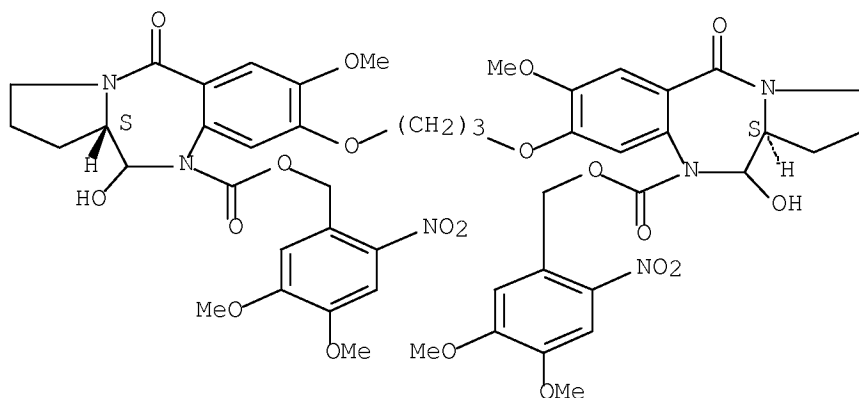
RN 260391-43-3 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis[(4-nitrophenyl)methyl] ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



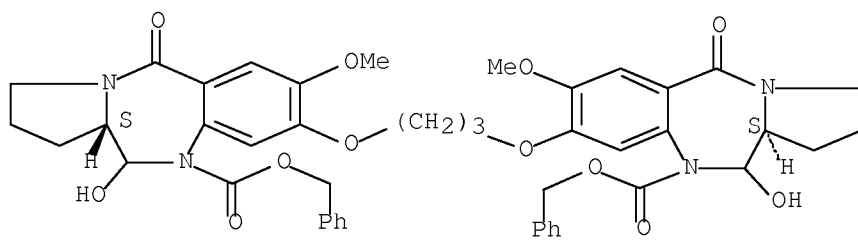
RN 260391-44-4 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis[(4,5-dimethoxy-2-nitrophenyl)methyl] ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



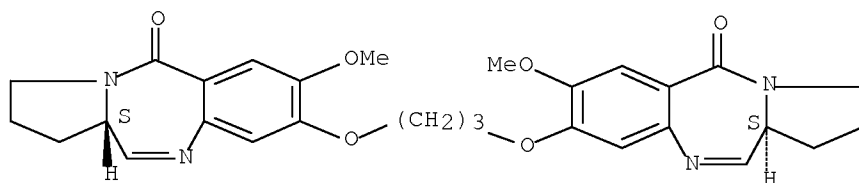
RN 260391-45-5 CAPLUS  
 CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,  
 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis(phenylmethyl) ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L18 ANSWER 69 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1999:676295 CAPLUS Full-text  
 DN 132:18480  
 TI Molecular modeling of a sequence-specific DNA-binding agent based on the pyrrolo[2,1-c][1,4]benzodiazepines  
 AU Adams, Lesley J.; Jenkins, Terence C.; Banting, Lee; Thurston, David E.  
 CS CRC Gene Targeted Drug Design Research Group, School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, PO1 2DT, UK  
 SO Pharmacy and Pharmacology Communications (1999), 5(9), 555-560  
 CODEN: PPCOFN; ISSN: 1460-8081  
 PB Royal Pharmaceutical Society of Great Britain  
 DT Journal  
 LA English  
 AB The CHARMM force field was used for the first time to model the tricyclic pyrrolobenzodiazepine (PBD) ring system. This system forms the core of the well known sequence-selective DNA-interactive anthramycin-type antitumor antibiotics. The results agreed with previous results obtained using the AMBER and X-PLOR force fields. The simple family member DC-81 preferentially binds in the 5S orientation with S-stereochem. at the C11 position of the PBD and with the A-ring of the mol. oriented towards the 5' end of the covalently bound strand. The modeling studies and energetic analyses also support the observation that the mols. have a sequence preference for the purine-guanine-purine motif.  
 IT 140676-21-7, DSB-120  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
 (mol. modeling of a sequence-specific DNA-binding agent based on the pyrrolo[2,1-c][1,4]benzodiazepines)  
 RN 140676-21-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

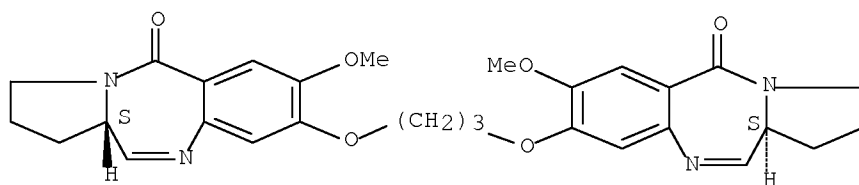
Absolute stereochemistry. Rotation (+).



RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 70 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1999:583940 CAPLUS Full-text  
 DN 132:89603  
 TI Design, Synthesis, and Evaluation of a Novel Sequence-Selective  
 Epoxide-Containing DNA Cross-Linking Agent Based on the  
 Pyrrolo[2,1-c][1,4]benzodiazepine System  
 AU Wilson, Stuart C.; Howard, Philip W.; Forrow, Stephen M.; Hartley, John  
 A.; Adams, Lesley J.; Jenkins, Terence C.; Kelland, Lloyd R.; Thurston,  
 David E.  
 CS CRC Gene Targeted Drug Design Research Group School of Pharmacy and  
 Biomedical Sciences, University of Portsmouth, Hants., PO1 2DT, UK  
 SO Journal of Medicinal Chemistry (1999), 42(20), 4028-4041  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 132:89603  
 AB Synthetic routes have been investigated to prepare a novel C8-epoxide-  
 functionalized pyrrolo[2,1-c][1,4]benzodiazepine 1 as a potential sequence-  
 selective DNA crosslinking agent (Wilson et al. Tetrahedron Lett. 1995, 36,  
 6333-6336). A successful synthesis was accomplished via a 10-step route  
 involving a pro-N10-Fmoc cleavage method that should have general  
 applicability to other pyrrolbenzodiazepine (PBD) mols. containing acid- or  
 nucleophile-sensitive groups. During the course of this work, a one-pot  
 reductive cyclization procedure for the synthesis of PBD N10-C11 imines from  
 nitro di-Me acetals was also discovered, although this method results in C11a  
 racemization which can reduce DNA binding affinity and cytotoxicity. The  
 target epoxide 1 was shown by thermal denaturation studies to have a  
 significantly higher DNA-binding affinity than the parent DC-81 or the C8-  
 propenoxy-PBD, which is structurally similar but lacks the epoxide moiety.  
 The time course of effects upon thermal denaturation indicated a rapid initial  
 binding phase followed by a slower phase consistent with the stepwise  
 crosslinking of DNA observed for a difunctional agent. This was confirmed by  
 an electrophoretic assay which demonstrated efficient induction of interstrand  
 cross-links in plasmid DNA at concns. >1  $\mu$ M. Higher levels of interstrand  
 crosslinking were observed at 24 h compared to 6 h incubation. A Taq  
 polymerase stop assay indicated a preference for binding to guanine-rich  
 sequences as predicted for bis-alkylation in the minor groove of DNA by  
 epoxide and imine moieties. The pattern of stop sites could be partly  
 rationalized by mol. modeling studies which suggested low-energy models to  
 account for the observed binding behavior. The epoxide PBD 1 was shown to  
 have significant cytotoxicity (45-60 nM) in the A2780, CH1, and CH1cisR human  
 ovarian carcinoma cell lines and an IC50 of 0.2  $\mu$ M in A2780cisR. The  
 significant activity of 1 in the cisplatin-resistant CH1cisR cell line (IC50 =  
 47 nM) gave a resistance factor of 0.8 compared to the parent cell line,  
 demonstrating no cross-resistance with the major groove crosslinking agent  
 cisplatin.  
 IT 140676-21-7, DSB 120  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES  
 (Uses)  
 (thermal stability with CT-DNA and in vitro cytotoxicity)  
 RN 140676-21-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
 propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

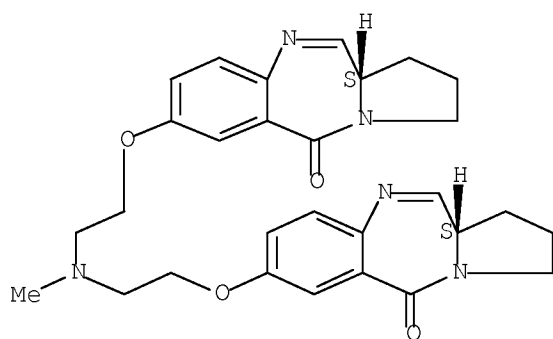


RE.CNT 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 71 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1999:346781 CAPLUS Full-text  
 DN 131:140917  
 TI Biological effects of a bifunctional DNA cross-linker. II. Generation of  
 micronuclei and attached micronuclear-like structures  
 AU Kurek, Kyle; Matsumoto, Lloyd; Gustafson, Gary; Pires, Richard;  
 Tantravahi, Umadevi; Suggs, J. William  
 CS Division of Biology and Medicine, Brown University, Providence, RI, 02912,  
 USA  
 SO Mutation Research, Fundamental and Molecular Mechanisms of Mutagenesis  
 (1999), 426(1), 89-94  
 CODEN: MUREAV; ISSN: 0027-5107  
 PB Elsevier Science B.V.  
 DT Journal  
 LA English  
 AB Madin-Darby bovine kidney (MDBK) cells were treated with the bifunctional DNA  
 cross-linker, L-7, to examine the generation of micronuclei and other nuclear  
 abnormalities. The preceding paper demonstrates that L-7 treatment induces  
 the formation of triradial and quadriradial chromosomes in MDBK cells. These  
 chromosomes are believed to result from interduplex DNA cross-links formed  
 between G-C rich centromeric satellite DNA regions on non-sister chromatids.  
 Treatment produces a majority of centromere-pos. micronuclei. In addition,  
 many daughter cells remain attached by chromatin bridges which are sometimes  
 beaded with micronuclei. Up to 15% of cell nuclei become lobular and fused  
 with numerous micronuclear-like structures attached to their membranes. These  
 attached structures are classified as attached micronuclear-like structures  
 (AMNLS). Fluorescence in situ hybridization (FISH) using a centromeric  
 satellite sequence was performed on treated cells. Hybridization reveals that  
 intercellular bridges are composed of centromeric sequences and initiate at  
 centromeric foci in daughter cells. Furthermore, the majority of junctions  
 between AMNLS and nuclei contain an enhancement of centromeric signal. The  
 frequency of AMNLS appears dependent on the concentration of L-7 and the  
 duration of treatment. Similar results were found for the generation of  
 cross-linked chromosome products in the previous paper. We suggest that AMNLS  
 result from the abnormal mitotic segregation of cross-linked chromosome  
 products.  
 IT 123064-64-2  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); BIOL (Biological study)  
 (biol. effects of bifunctional DNA cross-linker. II. Generation of  
 micronuclei and attached micronuclear-like structures)  
 RN 123064-64-2 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[(methylimino)bis(2,1-  
 ethanedioxy)]bis[1,2,3,11a-tetrahydro-, (11aS,11'aS)- (9CI) (CA INDEX  
 NAME)

Absolute stereochemistry.

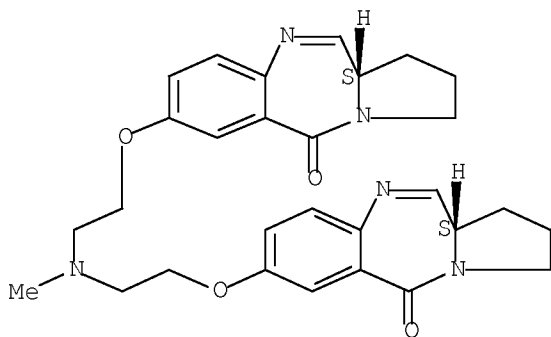




RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

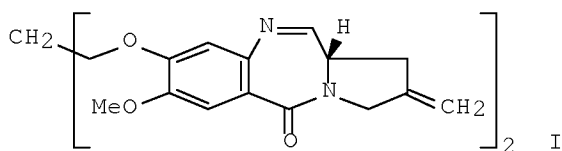
L18 ANSWER 72 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1999:346774 CAPLUS Full-text  
 DN 131:111396  
 TI Biological effects of a bifunctional DNA crosslinker. I. Generation of  
 triradial and quadriradial chromosomes  
 AU Matsumoto, L.; Kurek, K.; Larocque, K.; Gustafson, G.; Pires, R.; Zhang,  
 J.; Tantravahi, U.; Suggs, J. W.  
 CS Department of Biology, Rhode Island College, Providence, RI, 02908-1991,  
 USA  
 SO Mutation Research, Fundamental and Molecular Mechanisms of Mutagenesis  
 (1999), 426(1), 79-87  
 CODEN: MUREAV; ISSN: 0027-5107  
 PB Elsevier Science B.V.  
 DT Journal  
 LA English  
 AB Interduplex crosslinks by a bifunctional anthramycin DNA crosslinker produced  
 triradial and quadriradial chromosomes. The crosslinker alkylates guanine at  
 N-2. Bovine chromosomes contain GC-rich d. satellite DNAs at the centromeric  
 heterochromatin and is the basis for the formation of triradial and  
 quadriradial chromosomes at the centromeres. The in situ crosslinking of  
 interphase chromosomes indicates that the distance between centromeres is 17.5  
 Å. We conclude that the nuclear matrix associated DNA in the centromeric  
 heterochromatin of interphase chromosomes are positioned close enough for  
 crosslinking to occur. We propose a model for the generation of triradial and  
 quadriradial chromosomes based upon the number of interduplex crosslinks  
 between two chromosomes.  
 IT 123064-64-2  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); BUU (Biological use, unclassified); BIOL (Biological  
 study); USES (Uses)  
 (triradial and quadriradial chromosomes generated by the  
 DNA-crosslinking agent L-7)  
 RN 123064-64-2 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[(methylimino)bis(2,1-  
 ethanediylloxy)]bis[1,2,3,11a-tetrahydro-, (11aS,11'aS)- (9CI) (CA INDEX  
 NAME)

Absolute stereochemistry.



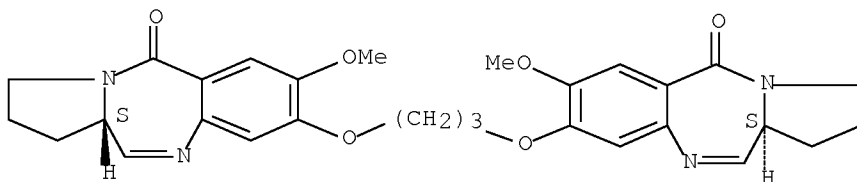
RE.CNT 30      THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 73 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1999:273645 CAPLUS Full-text  
 DN 131:116218  
 TI Synthesis of a novel C2/C2'-exo unsaturated pyrrolobenzodiazepine  
 cross-linking agent with remarkable DNA binding affinity and cytotoxicity  
 AU Gregson, Stephen J.; Howard, Philip W.; Thurston, David E.; Jenkins,  
 Terence C.; Kelland, Lloyd R.  
 CS School of Pharmacy and Biomedical Sciences, CRC Gene Targeted Drug Design  
 Research Group, University of Portsmouth, Portsmouth, Hants, PO1 2DT, UK  
 SO Chemical Communications (Cambridge) (1999), (9), 797-798  
 CODEN: CHCOFS; ISSN: 1359-7345  
 PB Royal Society of Chemistry  
 DT Journal  
 LA English  
 GI



AB A C2/C2'-exo unsatd. pyrrolobenzodiazepine dimer (I) has been synthesized  
 which is cytotoxic at the picomolar level and has remarkable covalent DNA  
 binding affinity, raising the melting temperature of duplex-form calf thymus  
 DNA by 34 after 18 h incubation.  
 IT 140676-21-7, DSB-120  
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological  
 process); BSU (Biological study, unclassified); BIOL (Biological study);  
 PROC (Process)  
 (preparation DNA binding and cytotoxicity of pyrrolobenzodiazepine  
 crosslinking agents towards ovarian cancer cells)  
 RN 140676-21-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
 propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



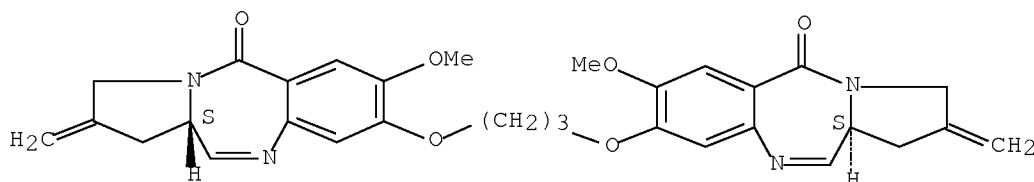
IT 232931-57-6P  
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological  
 process); BSU (Biological study, unclassified); SPN (Synthetic  
 preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)  
 (preparation DNA binding and cytotoxicity of pyrrolobenzodiazepine

crosslinking agents towards ovarian cancer cells)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 232931-64-5P

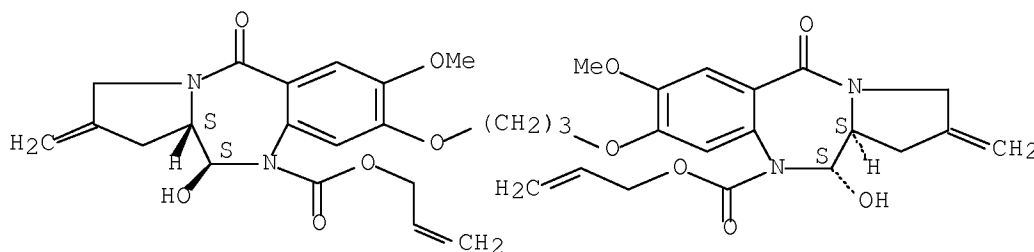
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation DNA binding and cytotoxicity of pyrrolobenzodiazepine crosslinking agents towards ovarian cancer cells)

RN 232931-64-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 232931-66-7P 232931-67-8P

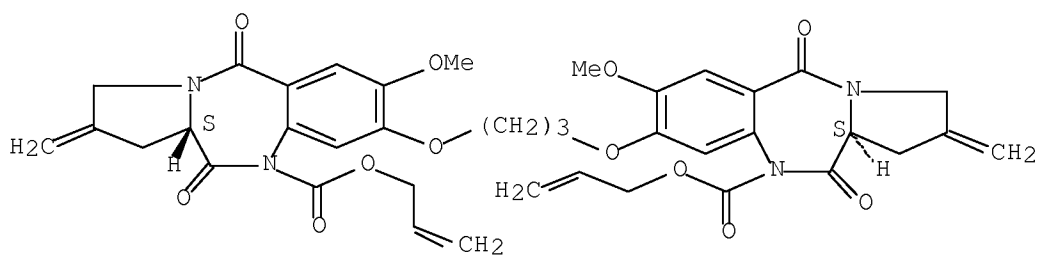
RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation DNA binding and cytotoxicity of pyrrolobenzodiazepine crosslinking agents towards ovarian cancer cells)

RN 232931-66-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-2-methylene-5,11-dioxo-, di-2-propenyl ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

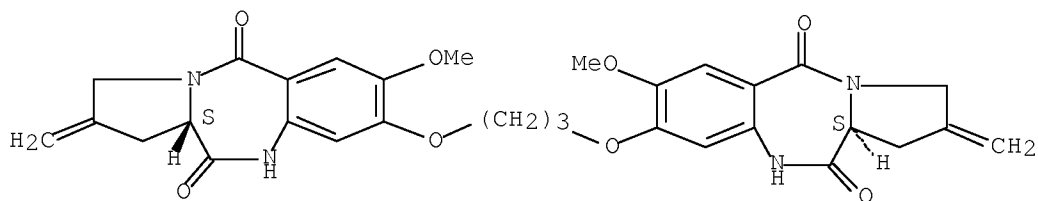
Absolute stereochemistry.



RN 232931-67-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione,  
8,8'-[1,3-propanediylbis(oxy)]bis[2,3-dihydro-7-methoxy-2-methylene-,  
(11aS,11'aS)- (9CI) (CA INDEX NAME)

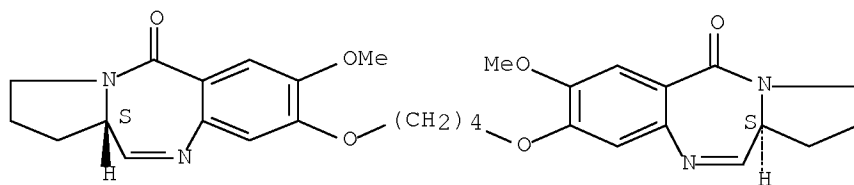
Absolute stereochemistry. Rotation (+).



RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

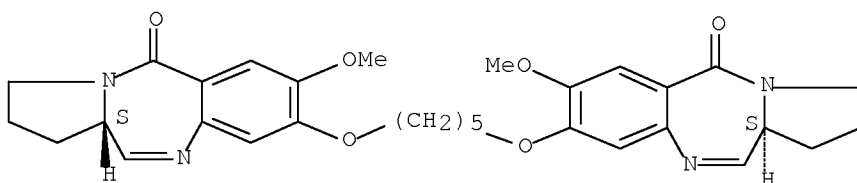
L18 ANSWER 74 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1996:644058 CAPLUS Full-text  
 DN 126:8088  
 TI Synthesis of Sequence-Selective C8-Linked Pyrrolo[2,1-  
 c][1,4]benzodiazepine Interstrand DNA Crosslinking Agents  
 AU Thurston, David E.; Bose, D. Subhas; Thompson, Andrew S.; Howard, Philip  
 W.; Leoni, Alberto; Croker, Stephen J.; Jenkins, Terrence C.; Neidle,  
 Steven; Hartley, John A.; Hurley, Laurence H.  
 CS School of Pharmacy and Biomedical Science, University of Portsmouth,  
 Portsmouth/Hants, PO1 2DT, UK  
 SO Journal of Organic Chemistry (1996), 61(23), 8141-8147  
 CODEN: JOCEAH; ISSN: 0022-3263  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 126:8088  
 AB An efficient convergent synthesis of a homologous series of C8-linked  
 pyrrolobenzodiazepine dimers with remarkable DNA interstrand crosslinking  
 activity and potent in vitro cytotoxicity is reported. The "amino thioacetal"  
 cyclization procedure was used to produce the electrophilic DNA-interactive  
 N10-C11 imine moiety during the final synthetic step. In order to construct  
 the key A-ring fragments, a versatile convergent approach has been developed  
 to join two units of vanillic acid with  $\alpha,\omega$ -dihaloalkanes of varying length to  
 provide the required bis(4-carboxy-2-methoxyphenoxy)alkanes while avoiding the  
 formation of mixts. of monoalkylated and bisalkylated products.  
 IT 145325-56-0P 145325-57-1P 145325-58-2P  
 183487-36-7P 183626-03-1P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of)  
 RN 145325-56-0 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-  
 butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA  
 INDEX NAME)

Absolute stereochemistry.



RN 145325-57-1 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-  
 pentanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
 (CA INDEX NAME)

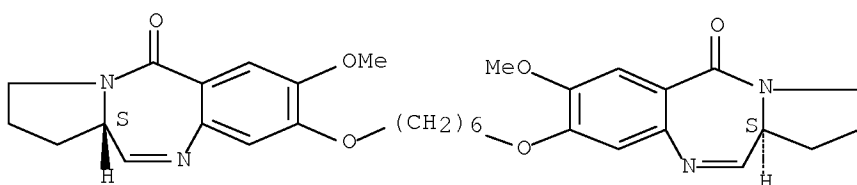
Absolute stereochemistry. Rotation (+).



RN 145325-58-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,6-hexanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

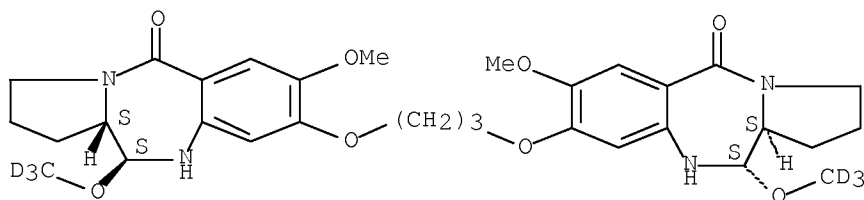
Absolute stereochemistry. Rotation (+).



RN 183487-36-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-11-(methoxy-d3)-, [11S-[8(11'R\*,11'aR\*),11α,11aα]]- (9CI) (CA INDEX NAME)

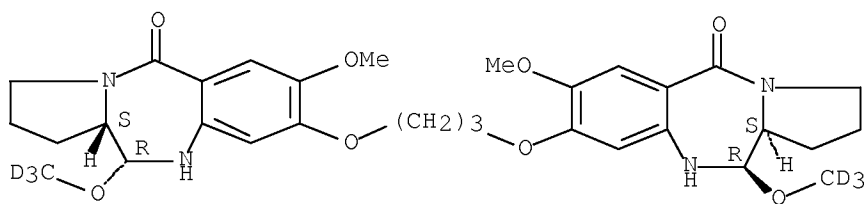
Absolute stereochemistry.



RN 183626-03-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-11-(methoxy-d3)-, [11R-[8(11'R\*,11'aS\*),11α,11aβ]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 140676-21-7P

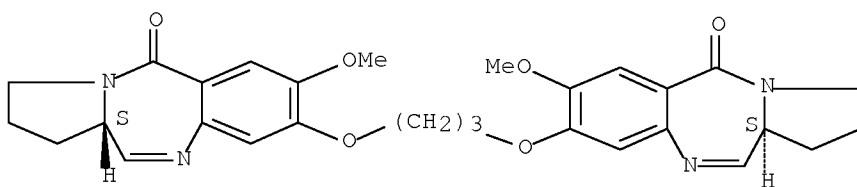
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(synthesis of sequence-selective C8-Linked pyrrolobenzodiazepine interstrand DNA crosslinking agents)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



L18 ANSWER 75 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 1996:550992 CAPLUS Full-text

DN 125:264974

TI Preclinical pharmacology and antitumor activity of the novel sequence-selective DNA minor-groove crosslinking agent DSB-120

AU Walton, M. I.; Goddard, P.; Kelland, L. R.; Thurston, D. E.; Harrap, K. R.

CS Institute Cancer Research, CRC Center Cancer Therapeutics, Belmont, SM2 5NG, UK

SO Cancer Chemotherapy and Pharmacology (1996), 38(5), 431-438

CODEN: CCPHDZ; ISSN: 0344-5704

PB Springer

DT Journal

LA English

AB In vitro cytotoxicity, antitumor activity, and preclin. pharmacokinetics of the novel sequence-selective, bifunctional alkylating agent DSB-120 (I), a synthetic pyrrolo[1,4][2,1-c]benzodiazepine dimer, was investigated. I was shown to be a potent cytotoxic agent against a panel of human colon carcinomas and two rodent tumors (L1210 and ADJ/PC6). The maximal antitumor effects were observed following a single i.v. dose but the therapeutic index was only 2.6. I was less effective when given i.p. either singly or by a daily x5 schedule. After a single i.v. dose at the maximum tolerated dose the plasma elimination was biphasic, with a short distribution phase being followed by a longer elimination phase. Concns. of I in ADJ/PC6 tumors were very low, showing a peak of 0.4 µg/g at 5 min. The steady-state tumor/plasma ratio was about 5% and the AUC was only 2.5% of that occurring in the plasma. I appeared to be unstable in vivo, with only 1% of an administered dose being recovered unchanged in 24 h urine samples. Plasma protein binding was extensive at 96.6%. In conclusion, the poor antitumor activity of I may be a consequence of low tumor selectivity and drug uptake as a result of protein binding and/or extensive drug metab in vivo.

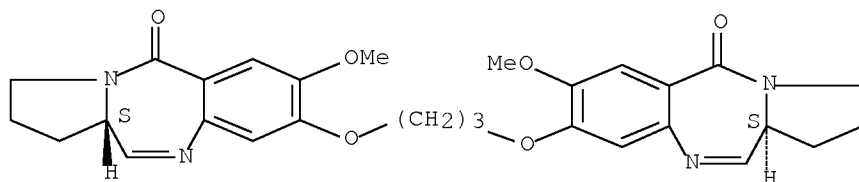
IT 140676-21-7

RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (preclin. pharmacol. and antitumor activity of DNA minor-groove crosslinking agent DSB-120)

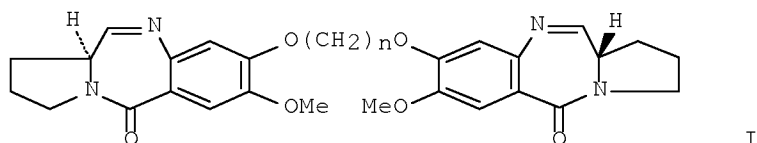
RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

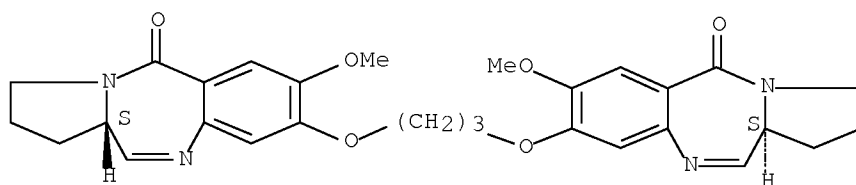


L18 ANSWER 76 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1995:637534 CAPLUS Full-text  
 DN 123:285962  
 OREF 123:51243a,51246a  
 TI Facile and efficient synthesis of the dimers of DC-81 antitumor antibiotics  
 AU Kamal, Ahmed; Rao, N. Venugopal  
 CS Div. Org. Chem., Indian Inst. Chem. Technol., Hyderabad, 500 007, India  
 SO Tetrahedron Letters (1995), 36(24), 4299-302  
 CODEN: TELEAY; ISSN: 0040-4039  
 PB Elsevier  
 DT Journal  
 LA English  
 OS CASREACT 123:285962  
 GI



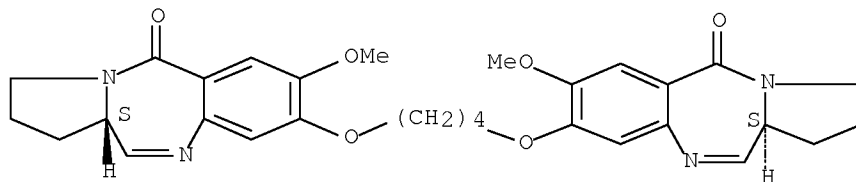
AB We report an improved, economical and versatile route to the dimers (I, n = 3, 4, 5) of DC-81 antitumor antibiotics. Particularly, the protection and deprotection steps in its synthesis and the preparation of its precursors have been avoided. There is a significant improvement in the overall yields.  
 IT 169436-02-6P 169436-03-7P 169436-04-8P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (synthesis of the dimers of DC-81 antitumor antibiotics)  
 RN 169436-02-6 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (R\*,R\*)- (9CI)  
 (CA INDEX NAME)

Relative stereochemistry.



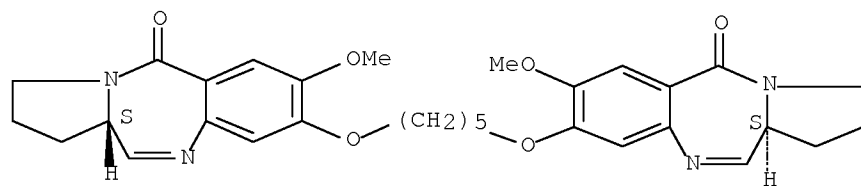
RN 169436-03-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (R\*,R\*)- (9CI)  
 (CA INDEX NAME)

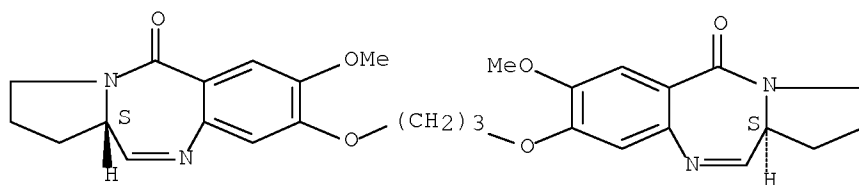
Relative stereochemistry.



RN 169436-04-8 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediybis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (R\*,R\*)- (9CI)  
 (CA INDEX NAME)

Relative stereochemistry.





L18 ANSWER 78 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 1995:50719 CAPLUS Full-text

DN 122:99738

OREF 122:18670h,18671a

TI Development of anthramycin-based sequence-selective DNA crosslinking agents

AU Jenkins, Terence C.; Neidle, Stephen; Thurston, David E.

CS Cancer Res. Campaign Biomolecular Structure Unit, Inst. Cancer Res., Sutton/Surrey, SM2 5NG, UK

SO Chem. Heterocycl. Compd., Proc. Symp., 11th (1993), 173-9. Editor(s): Stibor, Ivan. Publisher: Prague Inst. Chem. Technol., Prague, Czech. CODEN: 60BQAT

DT Conference

LA English

AB Mol. modeling techniques, using double-stranded DNA as a template, have been used to design a series of potent and novel DNA crosslinking agents with useful G/C recognition properties. DNA reactivity has been confirmed using biophys. and biochem. assays, and qual. structure-activity correlations for cytotoxic potency have been demonstrated. NMR solution studies provide a rational basis for the reactivity and DNA-crosslinking efficiency of the most reactive pyrrolobenzodiazepine dimer homolog, DSB-120. The predicted d(GATC) sequence preference for this agent, where the sequence contains a spanned ApT base tract, is substantiated by facile adduct formation with d(CICGATCICG).

IT 140676-21-7

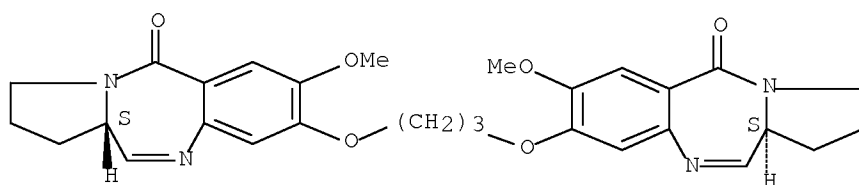
RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)

(pyrrolobenzodiazepine dimer homolog; development of anthramycin-based sequence-selective DNA crosslinking agents)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L18 ANSWER 79 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 1994:671426 CAPLUS Full-text

DN 121:271426

OREF 121:49267a,49270a

TI Cellular pharmacology of novel C8-linked anthramycin-based  
sequence-selective DNA minor groove cross-linking agents

AU Smellie, M.; Kelland, L.R.; Thurston, D.E.; Souhami, R.L.; Hartley, J.A.

CS School, UCL Medical, London, W1P 8BT, UK

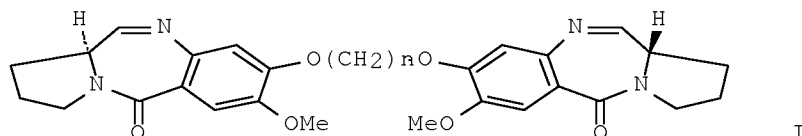
SO British Journal of Cancer (1994), 70(1), 48-53

CODEN: BJCAAI; ISSN: 0007-0920

DT Journal

LA English

GI



AB The cellular pharmacol. of a series of C8-linked pyrrolobenzodiazepine dimers with polymethylene linkers I ( $n = 3-6$ ) has been studied in a range of human tumor cell lines. The four compds. showed the same pattern of relative activity in five ovarian carcinoma cell lines and one cervical carcinoma cell line, which correlated with the previously demonstrated DNA interstrand crosslinking ability of the compds. in plasmid DNA. In human leukemic K562 cells the agents produced a block in the G2/M phase of the cell cycle characteristic of crosslinking drugs, and extensive interstrand crosslinking was observed in cells by alkaline elution with no evidence of single-strand breaks. Cross-links continued to increase up to 24 h following a 1 h exposure to drug, and no repair was evident by 48 h. In a series of ovarian and cervical carcinoma cell lines with acquired resistance to cisplatin no cross-resistance to the most potent compound I ( $n = 3$ ) was observed in two lines whose major mechanism of resistance to cisplatin was reduced platinum transport. Cross-resistance to 1 was observed in a cell line (A2780cisR) possessing elevated glutathione, and depletion of intracellular glutathione using D,L-buthionine-S,R-sulfoximine (BSO) from 10.25 nmol to 2.8 nmol 10-6 cells reduced the level of resistance from 11-fold to 2-fold compared with sensitive cells. Crosslinking in the resistant cells was restored to 80% of the level in the parent line by BSO pretreatment. There was also a correlation between glutathione levels and sensitivity to 1 measured in several other ovarian cell lines. I ( $n = 3$ ) also showed cross-resistance in the doxorubicin-resistance cell line 41MdoxR and partial cross-resistance in CHldoxR cells. Both these lines possess elevated levels of p170 glycoprotein. Following treatment with 6  $\mu$ M verapamil, the resistance in these lines decreased almost 2-fold and 8-fold resp.

IT 140676-21-7 145325-56-0 145325-57-1  
145325-58-2

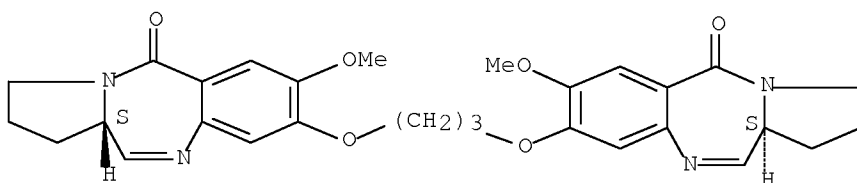
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(cellular pharmacol. of novel C8-linked anthramycin-based  
sequence-selective DNA minor groove crosslinking agents)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-  
propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
(CA INDEX NAME)

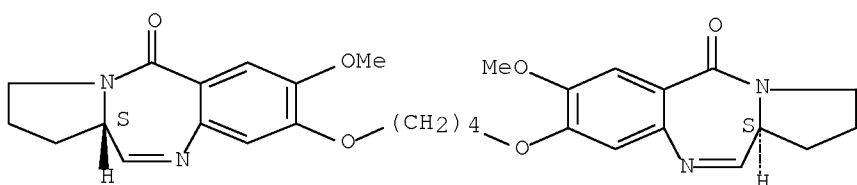
Absolute stereochemistry. Rotation (+).



RN 145325-56-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

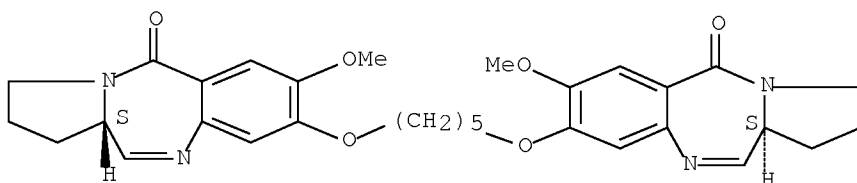
Absolute stereochemistry.



RN 145325-57-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediyldis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

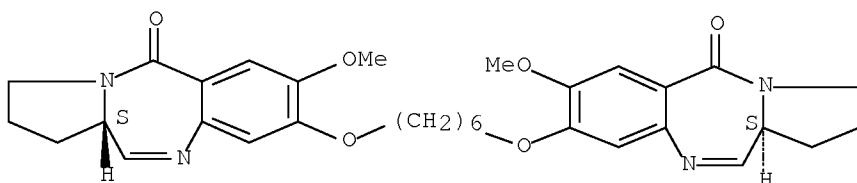
Absolute stereochemistry. Rotation (+).



RN 145325-58-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,6-hexanediyldis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).







L18 ANSWER 80 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 1994:270468 CAPLUS Full-text

DN 120:270468

OREF 120:47926h,47927a

TI Anticancer pyrrolo[2,1-c][1,4]benzodiazepines

IN Thurston, David Edwin; Bose, Deverakonda Subhas

PA Cancer Research Campaign Technology Ltd., UK

SO PCT Int. Appl., 49 pp.

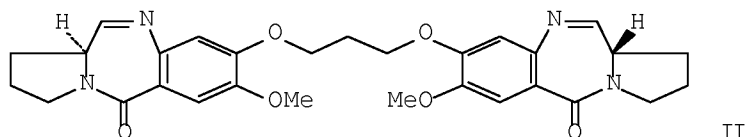
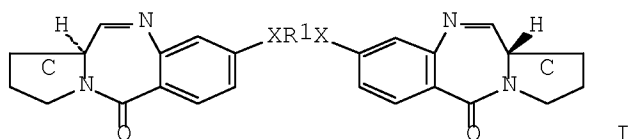
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 9318045	A1	19930916	WO 1993-GB483	19930308
	W: AU, CA, JP, RU, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	ZA 9301637	A	19931004	ZA 1993-1637	19930308
	AU 9336435	A	19931005	AU 1993-36435	19930308
PRAI	GB 1992-5051	A	19920309		
	WO 1993-GB483	A	19930308		
OS	MARPAT 120:270468				
GI					



AB The title compds. I [R1 = (un)substituted C3-12 alkylene; X = O, S, NH; the pyrrolobenzodiazepine ring may contain addnl. substituents in  $\geq 1$  of the 1, 2, 3, 6, 7, 9, and 11 positions and the C rings may optionally contain  $\geq 1$  addnl. hetero ring atom], which are capable of crosslinking double-stranded DNA and which are useful as anticancer agents, are prepared Thus, pyrrolobenzodiazepine II, prepared from vanillic acid in 7 steps, demonstrated 50% inhibitory concentration against L1210 mouse leukemia cells of 0.01  $\mu\text{M}$  and against ADJ/PC6 mouse plasma plasmacytoma of 0.0005  $\mu\text{M}$ .

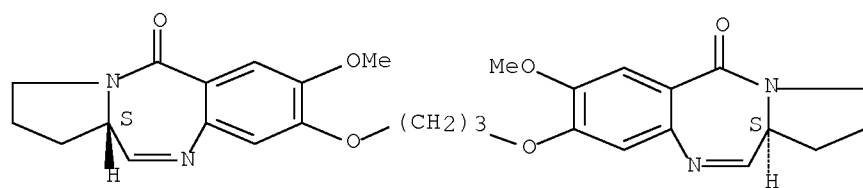
IT 140676-21-7P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation and anticancer activity of)

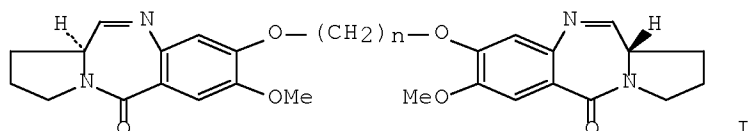
RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L18 ANSWER 81 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1993:59681 CAPLUS Full-text  
 DN 118:59681  
 OREF 118:10711a,10714a  
 TI Effect of linker length on DNA-binding affinity, cross-linking efficiency and cytotoxicity of C8-linked pyrrolobenzodiazepine dimers  
 AU Bose, D. Subhas; Thompson, Andrew S.; Smellie, Melissa; Berardini, Mark D.; Hartley, John A.; Jenkins, Terence C.; Neidle, Stephen; Thurston, David E.  
 CS Sch. Pharm. Biomed. Sci., Univ. Portsmouth, Portsmouth, PO1 2DZ, UK  
 SO Journal of the Chemical Society, Chemical Communications (1992), (20), 1518-20  
 CODEN: JCCCAT; ISSN: 0022-4936  
 DT Journal  
 LA English  
 OS CASREACT 118:59681  
 GI

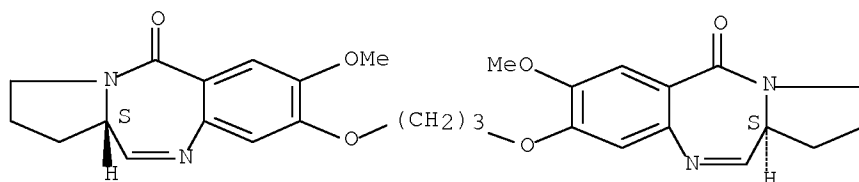


AB An efficient synthesis of a homologous series of C8-linked pyrrolobenzodiazepine dimers I ( $n = 3-6$ ) in 8 steps starting from vanillic acid is reported. I ( $n = 3, 5$ ), with an odd number of methylenes in the linker show a higher affinity for DNA, enhanced crosslinking efficiency, and are more cytotoxic compared with I ( $n = 4, 6$ ).

IT 140676-21-7P 145325-56-0P 145325-57-1P  
 145325-58-2P  
 RL: ADV (Adverse effect, including toxicity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (preparation and binding with DNA and cytotoxicity of)

RN 140676-21-7 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA INDEX NAME)

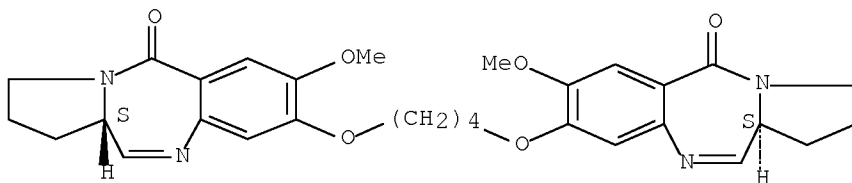
Absolute stereochemistry. Rotation (+).



RN 145325-56-0 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (CA

INDEX NAME)

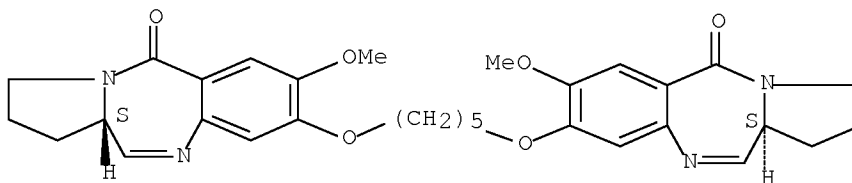
Absolute stereochemistry.



RN 145325-57-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediy]bis(oxy)bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

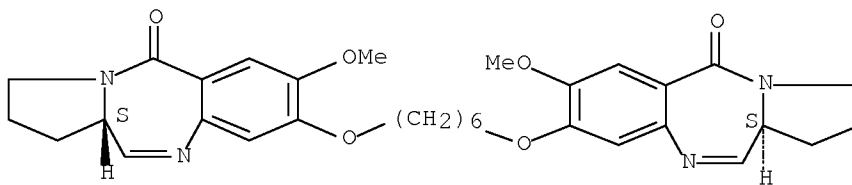
Absolute stereochemistry. Rotation (+).



RN 145325-58-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,6-hexanediyl]bis(oxy)bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L18 ANSWER 82 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 1992:483006 CAPLUS Full-text

DN 117:83006

OREF 117:14259a,14262a

TI Template-directed design of a DNA-DNA crosslinker based upon a bis-tomaymycin-duplex adduct

AU Wang, Jeh Jeng; Hill, G. Craig; Hurley, Laurence H.

CS Coll. Pharm., Univ. Texas, Austin, TX, 78712, USA

SO Journal of Medicinal Chemistry (1992), 35(16), 2995-3002

CODEN: JMCMAR; ISSN: 0022-2623

DT Journal

LA English

AB A template-directed approach to the design of a DNA-DNA interstrand cross-linker based upon the structure of a bis-tomaymycin-duplex adduct has been carried out. Tomaymycin is a member of the pyrrolo[1,4]benzodiazepines antitumor antibiotics. In a previous study it was shown that two tomaymycin mols. can be covalently bound to a 12-mer duplex mol., where the drug mols. are on opposite strands six base-pairs apart, and the stereochem. at the drug bonding site, and orientation in the minor groove, was defined by high-field NMR. This bis-tomaymycin 12-mer duplex adduct maintains the self-complementarity of the duplex and a B-type structure. In the present study it was shown using high-field NMR that this same 12-mer sequence can be truncated by two base pairs so that the two tomaymycin-modified guanines are now only four base-pairs apart, the two species of tomaymycin mols. are still bound with the same stereochem. and orientation, and the 10-mer duplex adduct maintains its self-complementarity. In a second 10-mer duplex it was shown that changing the bonding sequence from 5'CGA to 5'AGC does not significantly affect the structure of the bis-tomaymycin-duplex adduct. However, when the sequence is rearranged so that the drugs point in a tail-to-tail orientation rather than in the previous head-to-head configuration, there are more than one species of tomaymycin bound to DNA, and, as a consequence, the bis-tomaymycin 10-mer duplex adduct loses its self-complementarity. The 10-mer duplex containing the 5'CGA sequence, in which the tomaymycin mols. are oriented head to head was used to design an interstrand crosslinking species in which the two drug mols. are linked together with a flexible linker mol.

IT 140676-21-7

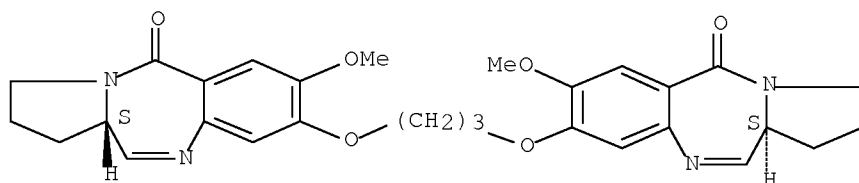
RL: BIOL (Biological study)

(as DNA-DNA interstand crosslinker, design of, tomaymycin-deoxyoligonucleotide adduct in relation to)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L18 ANSWER 83 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 1992:255585 CAPLUS Full-text

DN 116:255585

OREF 116:43339a,43342a

TI Rational design of a highly efficient irreversible DNA interstrand cross-linking agent based on the pyrrolobenzodiazepine ring system

AU Bose, D. Subhas; Thompson, Andrew S.; Ching, Jingshan; Hartley, John A.; Berardini, Mark D.; Jenkins, Terence C.; Neidle, Stephen; Hurley, Laurence H.; Thurston, David E.

CS Sch. Pharm. Biomed. Sci., Portsmouth Polytech., Portsmouth, PO1 2DZ, UK

SO Journal of the American Chemical Society (1992), 114(12), 4939-41

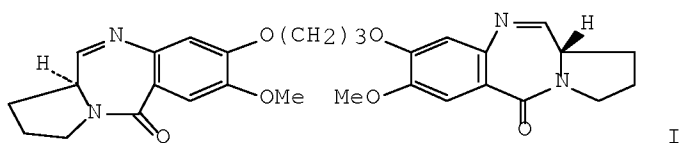
CODEN: JACSAT; ISSN: 0002-7863

DT Journal

LA English

OS CASREACT 116:255585

GI



AB Pyrrolo[2,1-c][1,4]benzodiazepine C8 dimer DSB-120 (I) was prepared and its DNA binding studied. I is a remarkably efficient crosslinking agent, showing activity down to at least 0.01  $\mu$ M and >90% crosslinking at 0.4  $\mu$ M. Extensive modeling studies of I with d(CGYGXXCYCG)2 show that the spatial separation of the pyrrolobenzodiazepine units is optimal for spanning 6 base pairs with a preference for 5'-PuGATCPy or 5'-PyGATCPu sequences, and that it actively recognizes the embedded d(GTAC)2 sequence. <sup>1</sup>H NMR of the 1:1 adduct of I and the self-complementary 10-mer d(CICGATCICG)2 showed that the duplex is crosslinked sym. via the minor groove N2 positions of the guanines, with 11S,11S' stereochem. in the ligand, and minor distortion of the helix.

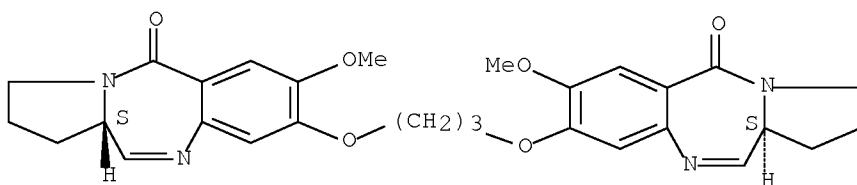
IT 140676-21-7P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation, antitumor, and DNA binding activities of)

RN 140676-21-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L18 ANSWER 84 OF 84 CAPLUS COPYRIGHT 2008 ACS on STN

AN 1989:573848 CAPLUS Full-text

DN 111:173848

OREF 111:28954h,28955a

TI Synthesis and DNA crosslinking ability of a dimeric anthramycin analog

AU Farmer, J. Dean, Jr.; Rudnicki, Suzanne M.; Suggs, J. William

CS Dep. Chem., Brown Univ., Providence, RI, 02912, USA

SO Tetrahedron Letters (1988), 29(40), 5105-8

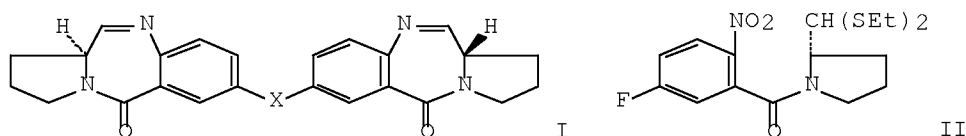
CODEN: TELEAY; ISSN: 0040-4039

DT Journal

LA English

OS CASREACT 111:173848

GI



AB Linked analogs I [X = S(CH<sub>2</sub>)<sub>6</sub>S, OCH<sub>2</sub>CH<sub>2</sub>NMeCH<sub>2</sub>CH<sub>2</sub>O] of the DNA binding antibiotic anthramycin are made via nucleophilic aromatic substitution of benzoylpyrrolidinecarboxaldehyde derivative II followed by reduction-cyclization. The linked compds. protect DNA from restriction endonucleases and reversibly crosslink DNA.

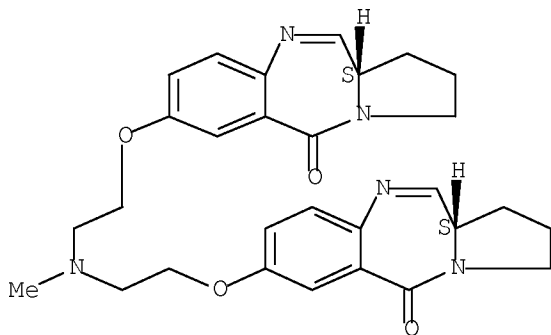
IT 123064-64-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)(preparation and DNA crosslinking by)

RN 123064-64-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[(methylimino)bis(2,1-ethanediyloxy)]bis[1,2,3,11a-tetrahydro-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



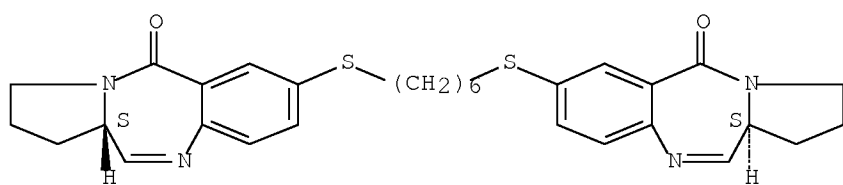
IT 123064-63-1P

RL: SPN (Synthetic preparation); PREP (Preparation)(preparation of)

RN 123064-63-1 CAPLUS

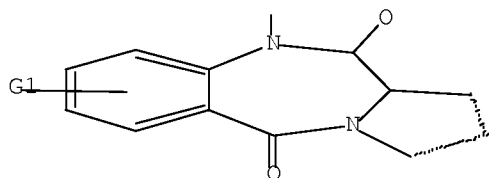
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[1,6-hexanediyloxy]bis(thio)]bis[1,2,3,11a-tetrahydro-, [S-(R\*,R\*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.





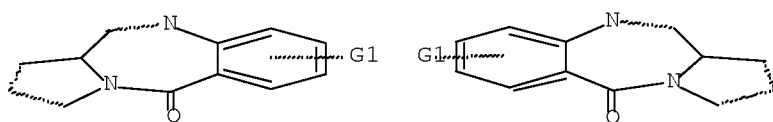
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 L2 HAS NO ANSWERS  
 L1 STR



G1 O, S, N

Structure attributes must be viewed using STN Express query preparation.  
 L2 QUE ABB=ON PLU=ON L1

L15 HAS NO ANSWERS  
 L14 STR



G1 O, S, N

Structure attributes must be viewed using STN Express query preparation.  
 L15 QUE ABB=ON PLU=ON L14

(FILE 'HOME' ENTERED AT 14:39:31 ON 20 MAY 2008)

FILE 'REGISTRY' ENTERED AT 14:39:58 ON 20 MAY 2008

L1 STRUCTURE UPLOADED  
 L2 QUE L1  
 L3 9 S L2  
 L4 281 S L2 FUL  
 L5 STRUCTURE UPLOADED  
 L6 QUE L5  
 L7 15 S L6  
 L8 239 S L6 FUL  
 L9 520 S L4 OR L8

FILE 'CAPLUS' ENTERED AT 14:42:41 ON 20 MAY 2008

L10 132 S L9  
 L11 46 S L4

FILE 'STNGUIDE' ENTERED AT 14:43:46 ON 20 MAY 2008

FILE 'REGISTRY' ENTERED AT 14:49:29 ON 20 MAY 2008

L12 STRUCTURE UPLOADED  
 L13 QUE L12  
 L14 STRUCTURE UPLOADED  
 L15 QUE L14  
 L16 19 S L15  
 L17 285 S L15 FUL

FILE 'CAPLUS' ENTERED AT 14:51:11 ON 20 MAY 2008

L18 84 S L17

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	712.34	1251.49
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-104.00	-104.00

STN INTERNATIONAL LOGOFF AT 14:55:54 ON 20 MAY 2008